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Question 1 of 414 ✓

A 73-year-old woman is referred to the endocrinology team with hypercalcemia.

Her blood results are shown below:

Calcium	2.89 mmol/L	(2.1-2.6)
Magnesium	0.9 mmol/L	(0.7-1.0)
Bilirubin	9 µmol/L	(3 - 17)
ALP	277 u/L	(30 - 100)
ALT	15 u/L	(3 - 40)
Î³GT	35 u/L	(8 - 60)
Albumin	42 g/L	(35 - 50)
PTH	0.4 pmol/L	(1.6-6.9)

What is the most likely cause of her hypercalcemia?

Malignancy	46%
Osteomalacia	7%
Paget's disease of the bone	22%
Primary hypoparathyroidism	12%
Secondary hypoparathyroidism	13%

In hypercalcaemia secondary to malignancy, PTH is low, although PTHrP may be raised

Important for me Less important

Malignancy is correct. This patient has hypercalcemia but a low PTH. The calcium is raised due to the presence of PTH-related protein (PTHrP) which is usually due to a malignancy. PTHrP is not detected when testing for PTH levels and requires a separate test.

Osteomalacia is incorrect. Osteomalacia is due to vitamin D deficiency in adults. Low vitamin D causes a *decrease* in serum calcium and phosphate. To compensate for this, there is a resultant increase in parathyroid hormone, producing secondary hyperparathyroidism.

Paget's disease of the bone is incorrect. Paget's disease of the bone is characterized by increased bone turnover resulting in enlarged and brittle bones. Blood tests would usually only show an isolated, raised ALP. The calcium should be normal.

Primary hypoparathyroidism is incorrect. This is due to failure of the parathyroid glands, resulting in low PTH and *low* calcium.

Secondary hypoparathyroidism is incorrect. This is a loss of PTH due to irradiation of the parathyroid gland, surgical removal of the gland, or low serum magnesium. This would result in low PTH and *low* calcium.

👍 | 👎 | 💬 Discuss (1) | Improve

Next question

Hypercalcaemia: causes ★

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
  - PTHrP from the tumour e.g. squamous cell lung cancer
  - bone metastases
  - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include

- sarcoidosis
  - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:

    - thiazides
    - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
    - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

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Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€“ presentation and management

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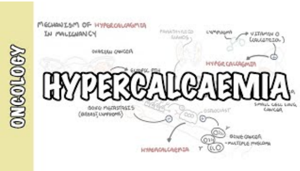
Media


ONCOLOGY
MECHANISM OF HYPERCALCAEMIA IN MALIGNANCY
HYPERCALCAEMIA

Hypercalcemia in malignancy

Armando Hasudungan - YouTube 👍 19 👎 2

PassMedicine

Question 2 of 414 ✓

A 72-year-old male is seen in clinic complaining of pain in both feet. He reports the pain is burning in nature and worse at night when sitting watching TV. It can often be severe and he is struggling to manage this with paracetamol alone. He has a past medical history of poorly controlled diabetes, hypertension and high cholesterol. On examination, he has normal power bilaterally but reduced sensation. Pedal pulses are present and there are no vascular related skin changes.

What is the most appropriate first line treatment for his pain?

Tramadol	3%
Topical capsaicin	8%
Codeine	2%
Duloxetine	83%
Naproxen	4%

First line treatment in diabetic neuropathy is with amitriptyline, duloxetine, gabapentin or pregabalin

Important for me Less important

The correct answer is duloxetine. This patient has a history of poorly controlled diabetes and combined with the examination findings of reduced sensation and normal pulses a diagnosis of diabetic neuropathy is most likely. NICE guidelines suggest first-line treatment for diabetic neuropathy is the same as for other causes of neuropathic pain with amitriptyline, duloxetine, gabapentin or pregabalin.

Topical capsaicin can be used for localised neuropathic pain such as postherpetic neuralgia but would not be first-line for this patient.

Tramadol is also not the first line treatment but can be used as rescue therapy for exacerbations.

Neither codeine or naproxen are recommended in neuropathic pain.

👍 👎 Discuss (2) Improve

Next question

Diabetic neuropathy

Peripheral neuropathy

Diabetes typically leads to sensory loss and not motor loss. Sensory loss typically results in a 'glove and stocking' distribution, with the lower legs affected first due to the length of the sensory neurons supplying this area. Painful diabetic neuropathy is also a common problem in clinical practice.

NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

Gastrointestinal autonomic neuropathy

Gastroparesis

- occurs secondary to autonomic neuropathy
- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

Chronic diarrhoea

- often occurs at night

Gastro-oesophageal reflux disease

- caused by decreased lower esophageal sphincter (LES) pressure

Next question

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Links

NICE 👍 2 👎 0

2013 Neuropathic pain guidelines

NICE 👍 0 👎 1

2022 Type 2 diabetes guidelines

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Score: **100%**

1 ✓
2 ✓

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Question 3 of 414 ✓

A 38-year-old woman is reviewed in the Endocrinology clinic, having been referred by her GP for refractory hypertension. Her ambulatory blood pressure readings have consistently been over 170/95 mmHg, in spite of gradual uptitration of amlodipine, enalapril and indapamide. She has no significant past medical history or family history, and examination of the chest and abdomen is normal.

Her blood test results are shown below:

Na^+	144 mmol/L	(135 - 145)
K^+	3.1 mmol/L	(3.5 - 5.0)
Bicarbonate	32 mmol/L	(22 - 29)
Urea	5.4 mmol/L	(2.0 - 7.0)
Creatinine	75 µmol/L	(55 - 120)

Which of the following is the most likely underlying cause of her hypertension?

Adrenal carcinoma	1%
Adrenal adenoma (Conn's syndrome)	44%
Autoimmune adrenalitis	1%
Phaeochromocytoma	6%
Bilateral adrenal hyperplasia	49%

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Important for me Less important

The presence of hypertension with hypokalaemia and mild alkalosis (as evidenced by the raised bicarbonate) should make candidates consider hyperaldosteronism. Hyperaldosteronism can be seen alongside elevated glucocorticoid activity in the context of excessive ACTH secretion (e.g. in Cushing's disease), or in isolation, as is the case in this patient. Hyperaldosteronism can be primary, or secondary to overzealous renin secretion, e.g. by a tumour, or in response to renal artery stenosis. Amongst the option choices, only causes of primary hyperaldosteronism are given. Of these, the most common epidemiologically is bilateral adrenal hyperplasia, which underlies 60-70% of cases of primary hyperaldosteronism.

Aldosterone-producing adrenal carcinomas account for less than 1% of all cases of primary hyperaldosteronism.

Aldosterone-producing adenomas, which produce the clinical entity of Conn's syndrome, account for approximately one third of cases of primary hyperaldosteronism, making this option epidemiologically less probable.

Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency, which gives rise to the clinical entity of Addison's disease. This tends to present with hyperkalaemia rather than hypokalaemia, and in particular, postural hypotension rather than hypotension, due to mineralocorticoid deficiency.

A phaeochromocytoma is a rare cause of persistent hypertension. However, the hypertension associated with excessive catecholamine secretion would not explain the hypokalaemia and alkalosis seen in this patient.

👍 👎 💬 Discuss (4) Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes
- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

Features

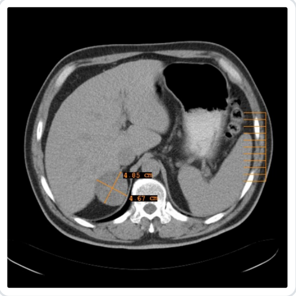
- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
  - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



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← Question 4 of 414 ✗ ⚑ →

A 57-year-old man with a known history of type-2 diabetes presents to clinic for a review. He currently takes metformin only for his diabetes and reports following the regime as instructed.

His HbA1c is 63 mmol/mol (target = 53mmol/mol) and the clinician and patient decide he should start a sulfonylurea in addition to his metformin.

Which of the following best describes the new treatment's mechanism of action?

Increases stimulation of insulin secretion by pancreatic B-cells and decreases hepatic clearance of insulin	80%
Inhibits sodium-glucose co-transporter-2 in the proximal convoluted tubule of the nephron to stop glucose reabsorption, meaning it is excreted in urine	4%
Inhibits the principal enzyme that breaks down GLP-1 - an incretin hormone that increases insulin secretion and suppresses glucagon secretion	3%
Reduces hepatic gluconeogenesis, increases peripheral glucose uptake and also reduces the absorption of carbohydrate in the gut	8%
Upregulation of transcription of insulin responsive genes, leading to an increase in glucose transporters and insulin receptors at the surface of the cell	5%

Sulfonyureas increase stimulation of insulin secretion by pancreatic B-cells and decrease hepatic clearance of insulin

Important for me Less important

The correct answer is option 1 as sulfonylureas are insulin secretagogues - one of the classes of oral hypoglycaemic agents. [1]

Option 2 best describes the mechanism of action of SGLT-2 inhibitors (dapagliflozin, canagliflozin). [2]

Option 3 best describes the mechanism of action of DPP-4 inhibitors (sitagliptin, vildagliptin).[3]

Option 4 best describes the mechanism of action of metformin, an insulin sensitiser.[4]

Option 5 best describes the mechanism of action of thiazolidinediones (pioglitazone), also an insulin sensitiser,[4]

According to NICE, metformin should be the first drug treatment of choice for those people who can tolerate it. The second medication, to be given in combination with metformin, can be any one of the four types of oral hypoglycaemic agents listed.[5]

1.) Sola, D., Rossi, L., Schianca, G., Maffioli, P., Bigliocca, M., Mella, R., CorlianÃ², F., Fra, G., Bartoli, E. and Derosa, G. (2015). State of the art paper Sulfonylureas and their use in clinical practice. Archives of Medical Science, 4, pp.840-848.
2.) Kalra, S. (2014). Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology. Diabetes Therapy, 5(2), pp.355-366.
3.) Vella, A. (2012). Mechanism of Action of DPP-4 Inhibitors'New Insights. The Journal of Clinical Endocrinology & Metabolism, 97(8), pp.2626-2628.
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5.) Nice.org.uk. (2018). Algorithm for blood glucose lowering therapy in adults with type 2 diabetes. [online] Available at: https://www.nice.org.uk/guidance/ng28/resources/algorithm-for-blood-glucose-lowering-therapy-in-adults-with-type-2-diabetes-pdf-2185604173 [Accessed 4 Oct. 2018].

Discuss (2) Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

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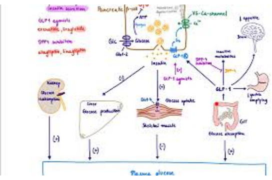
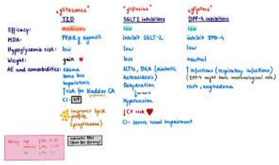


Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10



Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

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Question 5 of 414 ✗

An obese 37-year-old man is referred by his GP to a weight-loss and health class in an attempt to lose a significant amount of weight. The man is currently attending an education session on the glycaemic index of various foods and being advised to avoid those with a high glycaemic index.

Which of the following falls into this category?

	Boiled new potato	9%
	Brown rice	3%
🟥	Digestive biscuit	7%
	Fruit	6%
🟩	White rice	74%

A high glycaemic index food has a greater ability to raise blood glucose compared with glucose in normal glucose-tolerant individuals

Important for me Less important

From the above options, the correct answer is white rice - this is the only 'high glycaemic index (GI)' food listed, with a value of 87. Other examples of high GI foods include baked potatoes (85) and white bread (70).

The boiled new potato is classed as a medium GI food, with a value of 62.

Brown rice has a medium GI, with a lower value of 58, compared to white rice's value of 87.

Digestive biscuit also has a medium GI.

Fruits and vegetables are generally classed as low GI foods.

While exact glycemic indices of various foods should not be memorised, it is good to categorise foods into high, medium and low glycemic indices for the exam.

👍 👎 Discuss (6) Improve

Next question

Glycaemic index ★

The glycaemic index (GI) describes the capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals. Foods with a high GI may be associated with an increased risk of obesity and the post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

Classification	Examples
High GI	White rice (87), baked potato (85), white bread (80)
Medium GI	Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58), Porridge (55)
Low GI	Fruit and vegetables, peanuts

The glycaemic index is shown in brackets. Glucose, by definition, would have a glycaemic index of 100

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Question 6 of 414 ✗

A 75-year-old man is admitted to the ward with an infective exacerbation of COPD. He has reached the end of a 5-day course of prednisolone and doxycycline. He reports improvement, with his sputum returned to its normal colour, but he reports an ongoing productive cough and mild breathlessness. Chest auscultation reveals scanty crepitations. He was successfully weaned off oxygen therapy 12 hours ago.

His laboratory results are as follows:

Hb	165 g/L	Male: (135-180)
Platelets	220 * 10^9/L	(150 - 400)
WBC	12.5 * 10^9/L	(4.0 - 11.0)
Neuts	10.1 * 10^9/L	(2.0 - 7.0)
CRP	9 mg/L	(< 5)

What is the most likely cause of his abnormal blood test results?

	Acute myeloid leukaemia	1%
🟥	Chronic myeloid leukaemia	2%
🟩	Medication-induced neutrophilia	76%
	Hospital-acquired pneumonia	9%
	Persisting infection	12%

Corticosteroids can induce neutrophilia

Important for me Less important

The most likely cause of this patient's abnormal blood test results is **medication-induced neutrophilia** . Corticosteroids are known to induce neutrophilia, which in turn causes leukocytosis, by enhancing the survival of neutrophils within the circulation.

Persisting infection is less likely given the overall clinical context of the patient. While the patient has a persistent productive cough, dyspnoea, and some crepitations, this is common after an exacerbation of COPD and may take several weeks to resolve. The patient's general improvement, successful weaning off oxygen therapy, and only mildly elevated C-reactive protein, which is likely on a downward trajectory following treatment, further argue against ongoing infection.

Similarly, **hospital-acquired pneumonia** seems unlikely with the same clinical rationale given above.

Leukaemia is much less likely in this patient, given the context of the scenario and lack of mention of constitutional symptoms, organomegaly or pancytopenia.

👍 👎 Discuss (1) Improve

Next question

Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	Glucocorticoid activity, high mineralocorticoid activity,	Predominant glucocorticoid activity, low mineralocorticoid activity	Very high glucocorticoid activity, minimal mineralocorticoid activity
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

The side effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects

- endocrine
  - impaired glucose regulation
  - increased appetite/weight gain
  - hirsutism
  - hyperlipidaemia
- Cushing's syndrome
  - moon face
  - buffalo hump
  - striae
- musculoskeletal
  - osteoporosis
  - proximal myopathy
  - avascular necrosis of the femoral head
- immunosuppression
  - increased susceptibility to severe infection
  - reactivation of tuberculosis
- psychiatric
  - insomnia
  - mania
  - depression
  - psychosis
- gastrointestinal
  - peptic ulceration
  - acute pancreatitis
- ophthalmic
  - glaucoma
  - cataracts
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
- longer-term systemic corticosteroids suppress the natural production of endogenous steroids. They should therefore not be withdrawn abruptly, as this may precipitate an Addisonian crisis
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have:

  - received more than 40mg prednisolone daily for more than one week
  - received more than 3 weeks of treatment
  - recently received repeated courses

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Score: **50%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗

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Question 7 of 414 ×

A 32-year-old woman attends the endocrinology clinic with fatigue and constipation. She has a history of menorrhagia, Wolff-Parkinson-White syndrome, and primary hypothyroidism. Her thyroid function tests were satisfactory 6 months ago. Her drug history includes levothyroxine 100 micrograms (once daily at 7am), amiodarone 200mg (once daily at 7am), and ferrous fumarate 210mg (once daily at 7am).

Blood results are as follows:

Thyroid stimulating hormone (TSH)	24.2 mU/L	(0.5-5.5)
Free thyroxine (T4)	6.8 pmol/L	(9.0 - 18)

How will you manage this situation?

	Advise the patient to take iron tablets at least 2 hours apart from levothyroxine	13%
🟩	Advise the patient to take iron tablets at least 4 hours apart from levothyroxine	73%
	Counsel the patient on the consequences of poor compliance	3%
🟥	Discontinue amiodarone	5%
	Increase dose of levothyroxine	6%

Iron / calcium carbonate tablets can reduce the absorption of levothyroxine - should be given 4 hours apart

Important for me Less important

Advise the patient to take iron tablets at least 4 hours apart from levothyroxine is correct. The patient has poorly controlled hypothyroidism. The fact that the patient had normal thyroid function tests 6 months ago suggests that she is on the right dose, however, it is important to bear in mind that dose requirements can change. You should note that the patient is taking iron tablets at the same time as the levothyroxine. Iron inhibits levothyroxine absorption and this is the most likely explanation in this situation. The patient should be advised to take iron tablets at least 4 hours apart from levothyroxine, and she should be brought back for repeat thyroid function tests (TFTs) in 6 weeks.

Advise the patient to take iron tablets at least 2 hours apart from levothyroxine is incorrect. A minimum time of 4 hours between iron and levothyroxine is required to prevent poor absorption.

Counsel the patient on the consequences of poor compliance is incorrect. It would be important to consider compliance issues. However, in this case, poor absorption due to iron is the more likely cause. Patients with poor compliance will often take a 'loading dose' before attending for blood results resulting in an elevated fT4 and TSH. However, if they have not taken their thyroxine for many days then they may have a normal/low fT4.

Discontinue amiodarone is incorrect. Although amiodarone is a well-known cause of hypothyroidism, it is a less likely cause in this scenario since the patient is already on thyroid replacement (which is the treatment for amiodarone-induced hypothyroidism). Furthermore, there is a clear and well-recognised drug interaction between levothyroxine and iron which should be rectified in the first instance. It would also be essential to liaise with the patient's cardiologist before discontinuing the amiodarone.

Increase dose of levothyroxine is incorrect. Although the patient may ultimately need an increased dose, it would be essential to exclude drug-drug interactions, drug-food interactions, poor compliance, and malabsorption, before increasing the dose.

👍 👎 Discuss Improve

Next question

Hypothyroidism: levothyroxine therapy

Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value

- there is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions

- iron, calcium carbonate
    - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

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Clinical Knowledge Summaries 👍 7 👎 6

Management of hypothyroidism

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← Question 8 of 414 ✗ ⚐ →

A 38-year-old, with a raised BMI and confirmed type II diabetes is seen in the clinic for a review of his glucose control.

Despite already being initiated on treatment several months previously his home blood glucose readings and latest Hb1Ac remain high. It is decided that the patient is to be commenced on a gliclazide. The patient is warned that this new medication may induce hypoglycaemia as an adverse effect due to an increase in the production and release of insulin.

What pancreatic cell membrane channels does this new medication bind to?

🟩	ATP-dependent potassium	75%
	Dipeptidyl peptidase-4 (DDP)	9%
	Ligand-gated chloride	5%
	Tyrosine kinase	7%
🟥	Voltage-gated calcium	4%

Sulfonylureas - bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells

Important for me Less important

Gliclazide is a sulfonylurea antidiabetic drug whose mechanism of action is via the increased release of insulin from the pancreatic beta cells. Sulfonylureas bind to and close **ATP-dependent potassium** channels on these beta cells, depolarising them. This results in an increase in intracellular calcium, due to the opening of calcium channels, which in turn increases the secretion of insulin.

Dipeptidyl peptidase-4 (DDP) is a type of enzyme, not a membrane channel, that affects glucose metabolism. DDP inhibitors, used in the management of diabetes, increase levels of incretin such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which in turn result in an increase in insulin secretion, decrease in gastric emptying and therefore a decrease in blood glucose levels.

Chloride channels are involved in several regulatory functions within the body including the transport of epithelial fluid in the lung, pancreas and other organs. These channels are not affected by sulfonylureas.

Insulin binds to **tyrosine kinase**, a type of enzyme receptor in the cell membrane, resulting in a signal transduction cascade, activating enzymes and transcription factors within the cell that mediates the intracellular effects of insulin. Again, sulfonylureas do not affect these receptors.

Voltage-gated calcium channels are opened within pancreatic beta cells resulting in the release of insulin however they are not directly bound to by sulfonylureas. Instead, it is the depolarising effect of sulfonylureas binding to ATP-dependent potassium channels which opens these calcium channels.

👍 | 👎 | 💬 Discuss (2) | Improve

Next question

Sulfonylureas ★

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

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← Question 9 of 414 ✓ →

A 27-year-old man presents to his general practitioner with his wife due to an inability to conceive after 1 year of regular unprotected sexual intercourse. The patient's medical history is unremarkable.

Examination of the external genitalia reveals bilaterally low-volume testes and sparse pubic and axillary hair. Moderate gynecomastia is present bilaterally.

Semen analysis is significant for azoospermia.

The results of an endocrine panel are shown below:

Luteinising Hormone	22.3 IU/L	(1.2-8.6)
Follicle Stimulating Hormone	30 IU/L	(1.3-19.3)
Testosterone	3 nmol/L	(6 -27)

What is the most likely diagnosis?

Congenital androgen insensitivity syndrome	12%
Kallmann syndrome	14%
Klinefelter's syndrome	72%
Leydig cell tumour	1%
Pituitary adenoma	2%

Klinefelter's syndrome causes high LH and low testosterone

Important for me Less important

Klinefelter's syndrome is the correct answer. Klinefelter's syndrome, with karyotype 47XXY, is associated with primary hypogonadism in patients with male external genitalia. Patients with Klinefelter's syndrome may be unaware of their condition until they wish to start a family. General examination of patients with Klinefelter's syndrome may reveal tall stature, low-volume testes, sparse pubic hair, and gynecomastia. The condition is associated with hypergonadotrophic hypogonadism, in which FSH and LH concentrations are elevated and serum testosterone concentrations are low. Gonadal dysgenesis secondary to Klinefelter's syndrome impairs spermatogenesis, with semen analysis commonly showing azoospermia.

Congenital androgen insensitivity syndrome is incorrect. Patients with this condition are genetically male (46XY), yet are phenotypically female with female external genitalia due to a defect in the androgen receptor. The patient in this vignette has male external genitalia, excluding the diagnosis of congenital androgen insensitivity syndrome.

Kallmann syndrome is incorrect. Kallman syndrome is a pituitary disorder associated with an impaired sense of smell (anosmia) hypogonadotrophic hypogonadism. The condition is characterised by low concentrations of LH and FSH, in contrast to Klinefelter's syndrome, which is associated with increased concentrations of LH and FSH.

Leydig cell tumour is incorrect. Leydig cell tumours are sex-chord tumours of the testes or ovaries that secrete testosterone. Male patients commonly present with testicular swelling, which is not present in this patient.

Pituitary adenoma is incorrect. Pituitary tumours may rarely cause hypogonadotrophic hypogonadism, in which low concentrations of LH and FSH result in low testosterone, but the high concentrations of LH and FSH in this patient make this diagnosis unlikely.

👍 👎 Discuss (1) Improve

Next question

Klinefelter's syndrome

Klinefelter's syndrome is associated with karyotype 47, XXY.

Features
- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels but low testosterone

Diagnosis is by karyotype (chromosomal analysis).

Question 10 of 414 ✗

A 35-year-old man presents to his GP with a six-week history of weight gain, cold intolerance, low mood, and headaches. He has a past medical history of primary hyperparathyroidism and underwent parathyroidectomy one year ago.

The following blood tests have been arranged:

Thyroid-stimulating hormone (TSH)	2.3 mU/L	(0.5-5.5)
Free thyroxine (T4)	5.6 pmol/L	(9.0 - 18)
Prolactin	34 ng/mL (< 20)	

What is the most likely cause of the patient's symptoms?

	Hashimoto's thyroiditis	14%
	Hypothalamic dysfunction	13%
	Microprolactinoma	27%
🟩	Non-functioning pituitary adenoma	34%
🟥	Subacute thyroiditis	13%

The presence of an elevated prolactin level along with secondary hypothyroidism and hypogonadism is indicative of stalk compression is consistent with a non-functioning pituitary adenoma

Important for me Less important

In this scenario, the patient presents with clinical features of hypothyroidism, including weight gain, cold intolerance, and low mood. Thyroid function tests reveal a decreased T4 level alongside an inappropriately normal TSH level, suggesting a secondary aetiology for his symptoms. The most likely diagnosis is a pituitary adenoma, which is corroborated by the patient's headache complaints—a symptom attributable to dural irritation from an enlarging tumour. The patient's mildly elevated prolactin level suggests a **non-functioning pituitary adenoma** compressing the pituitary stalk rather than a prolactinoma, which would cause a greater rise. Non-functioning adenomas characteristically present with signs and symptoms resulting from mass effects, such as hypopituitarism due to compression of the intact pituitary gland tissue and bitemporal hemianopia caused by impingement of the optic chiasm.

Hypothalamic dysfunction typically manifests with hypopituitarism, presenting with some of the symptoms seen here, such as weight gain and cold intolerance due to hypothyroidism. However, it would not cause a raised prolactin.

Hashimoto's thyroiditis, as a primary cause of hypothyroidism, would be expected to elevate TSH levels—in contrast to what is observed in this patient. Hashimoto's thyroiditis is an autoimmune condition associated with anti-TPO antibodies.

It would be unusual for a **microprolactinoma** to induce hypopituitarism via compression exerted by the tumour on healthy pituitary tissue as they typically do not grow to a sufficient size. Furthermore, one would expect to observe an increased prolactin level (above 100 ng/mL). The modest elevation in prolactin noted here aligns more closely with stalk compression secondary to a non-functioning pituitary adenoma.

Subacute thyroiditis (also known as De Quervain's thyroiditis), presents after a viral infection with hyperthyroidism, both of which are absent in this case. As the condition progresses the patient develops hypothyroidism before returning to a euthyroid state. However, without a history of hyperthyroidism, this answer is very unlikely.

Discuss (1) Improve

Next question

Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:

- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)
- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
  - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:
- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:
- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of
- medical therapy:
  - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
  - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas
  - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery
  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line

treatment

- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Patient.info 👍 7 👎 0

Pituitary tumours review

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Score: **40%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗

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Question 11 of 414 ✗

Which of the following secondary causes of hyperlipidaemia result in predominantly hypercholesterolaemia, as opposed to hypertriglyceridaemia?

Diabetes mellitus	10%
Bendrofluazide	12%
🟩 Nephrotic syndrome	57%
🟥 Alcohol	9%
Obesity	12%

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

Important for me Less important

The correct answer is **Nephrotic syndrome**. Nephrotic syndrome is a kidney disorder that causes the body to excrete too much protein in the urine. This results in low levels of albumin and increased lipoprotein production, leading to hypercholesterolaemia (high cholesterol). The other forms of hyperlipidaemia, such as hypertriglyceridaemia, are not as prevalent.

Diabetes mellitus is an incorrect option because it primarily leads to hypertriglyceridaemia rather than hypercholesterolaemia. In diabetes mellitus, insulin resistance or deficiency results in decreased lipoprotein lipase activity and increased very low-density lipoprotein (VLDL) synthesis. This leads to elevated triglyceride levels.

Bendrofluazide, a thiazide diuretic used for hypertension, can indeed cause dyslipidaemia. However, it typically raises both cholesterol and triglyceride levels rather than causing predominantly hypercholesterolaemia.

Regarding **Alcohol**, chronic heavy consumption can lead to both hypertriglyceridaemia and hypercholesterolaemia due to increased VLDL secretion and decreased lipid clearance. However, it's more associated with raised triglycerides than cholesterol.

Finally, **Obesity** does not specifically result in predominantly hypercholesterolaemia. It's associated with a range of lipid abnormalities including elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and normal or slightly elevated low-density lipoprotein (LDL) cholesterol levels due to insulin resistance.

In summary, while all these options can cause some form of dyslipidaemia, only nephrotic syndrome is particularly known for causing predominantly hypercholesterolaemia.

Discuss (6) Improve

Next question

Hyperlipidaemia: secondary causes ★

Causes of predominantly hypertriglyceridaemia

- diabetes mellitus (types 1 and 2)
- obesity
- alcohol
- chronic renal failure
- drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- liver disease

Causes of predominantly hypercholesterolaemia

- nephrotic syndrome
- cholestasis
- hypothyroidism

Next question

Textbooks

PassMedicine

Question 12 of 414 ✓

A 19-year-old male presented to the andrology clinic with failure to gain secondary sexual characteristics. His height is 186 cm and his weight is 65 kg with a body mass index of 18.7 kg/m^2.

Investigations results are as follows:

Testosterone	6.2 nmol/L	(8.7 - 29)
FSH	0.3 u/L	(0.3 - 10.0)
LH	1.6 u/L	(1.7 - 8.6)

What is the most likely diagnosis?

Androgen insensitivity syndrome	7%
[✓ Kallmann syndrome]	61%
Klinefelter syndrome	27%
Testicular regression syndrome	1%
21-hydroxylase deficiency	3%

Kallman's syndrome - LH & FSH low-normal and testosterone is low

Important for me Less important

Kallmann syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. Patients are typically of normal or above-average height with anosmia. Sex hormone levels are low. LH, FSH levels are low/inappropriately normal.

Klinefelter syndrome (47,XXY) is the set of symptoms that result from two or more X chromosomes in males. The primary features are infertility and small poorly functioning testicles. It is characterised by low testosterone levels with increased levels of FSH and LH.

21-hydroxylase deficiency is due to congenital adrenal hyperplasia, characterised by virilisation of female genitalia and precocious puberty in males.

Androgen insensitivity syndrome is an X-linked recessive condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype.

Bilateral testicular regression syndrome is a very rare condition characterized by the absence of testicular tissue in a genotypic male. It is characterised by low testosterone levels with increased levels of FSH and LH.

Discuss (5) | Improve

Next question

Kallmann's syndrome ★

Kallmann's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallmann's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty.

Features
- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above-average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Management
- testosterone supplementation
- gonadotrophin supplementation may result in sperm production if fertility is desired later in life

Next question

PassMedicine

Question 13 of 414 ✗

Which one of the following is most likely to be found in a patient with Hashimoto's thyroiditis?

	Raised ESR	6%
🟥	Anti-TSH receptor stimulating antibodies	13%
🟩	Anti-thyroid peroxidase antibodies	77%
	Decreased TSH	3%
	Co-existing type 2 diabetes mellitus	3%

Hashimoto's thyroiditis = hypothyroidism + goitre + anti-TPO

Important for me Less important

The correct answer is **Anti-thyroid peroxidase antibodies**. Hashimoto's thyroiditis, also known as chronic lymphocytic thyroiditis, is primarily an autoimmune disorder. The hallmark of this condition is the presence of autoantibodies against thyroid-specific antigens, such as thyroid peroxidase (TPO) and thyroglobulin. Anti-TPO antibodies are the most common and are found in up to 90-95% of patients with Hashimoto's thyroiditis.

Raised ESR (Erythrocyte Sedimentation Rate) can be seen in various inflammatory conditions including systemic lupus erythematosus, rheumatoid arthritis, and infection. While inflammation does occur in Hashimoto's thyroiditis due to immune-mediated destruction of the thyroid gland, a raised ESR is not specific for this condition and would not be the most likely finding.

Anti-TSH receptor stimulating antibodies are typically associated with Graves' disease, another autoimmune disorder affecting the thyroid. These antibodies mimic the action of TSH (Thyroid-Stimulating Hormone), binding to its receptors on the surface of thyroid cells leading to overproduction of thyroid hormones (hyperthyroidism). In contrast, Hashimoto's disease often results in hypothyroidism due to destruction of the gland.

A **Decreased TSH** level is usually indicative of hyperthyroidism or excessive exogenous intake of thyroxine. In Hashimoto's disease, which often leads to hypothyroidism due to progressive destruction of the gland, one would expect an elevated TSH level as part of a compensatory mechanism by the pituitary gland attempting to stimulate more hormone production from a failing thyroid gland.

Finally, while there may be an increased prevalence of **Co-existing type 2 diabetes mellitus** in patients with autoimmune diseases like Hashimoto's due to shared genetic predisposition and immune dysregulation, it should not be considered a characteristic feature or diagnostic criterion for Hashimoto's Thyroiditis. Thus it isn't necessarily expected or 'most likely' in these patients compared to anti-TPO antibodies.

Discuss (3) | Improve

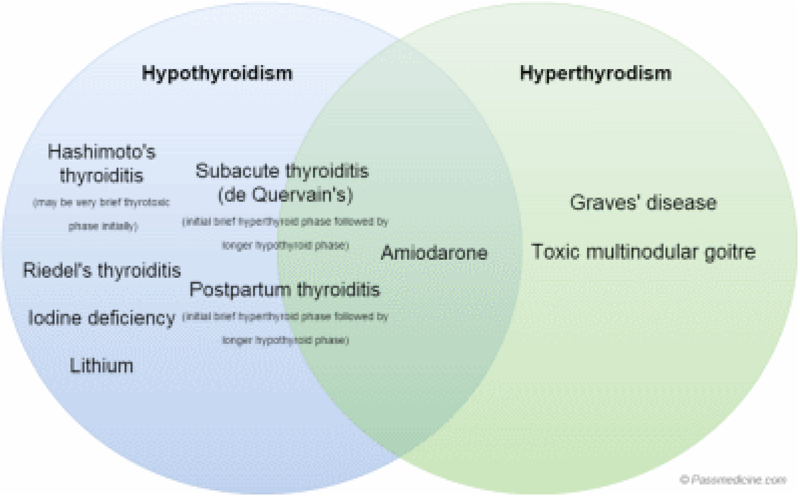
Next question

Hashimoto's thyroiditis ★

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features
- features of hypothyroidism
- goitre: firm, non-tender
- anti-thyroid peroxidase (TPO) and also anti-thyroglobulin (Tg) antibodies

Associations
- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of MALT lymphoma


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
Amiodarone
Graves' disease
Toxic multinodular goitre
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

Textbooks

High-yield textbook

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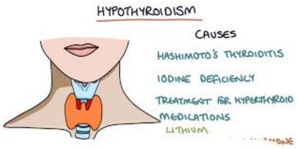
Media


HYPOTHYROIDISM
CAUSES
HASHIMOTO'S THYROIDITIS
IODINE DEFICIENCY
TREATMENT FOR HYPERTHYROID
MEDICATIONS
LITHIUM

Hypothyroidism and Hashimoto's Thyroiditis: Visual Explanation for Students

Zero To Finals - YouTube 👍 18 👎 1

Report broken media

Score: **38.5%**

1 ✓
2 ✓
3 ✓
4 ✗

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Question 14 of 414 ✓

You review a 21-year-old woman who has recently been diagnosed with type 1 diabetes mellitus. She was admitted three months ago with vomiting, abdominal pain and weight loss and was found to hyperglycaemic. A diagnosis of type 1 diabetes mellitus was made. She was started on insulin. Recent bloods show the following:

Na$^+$	140 mmol/l
K$^+$	3.8 mmol/l
Urea	3.4 mmol/l
Creatinine	72 µmol/l

Total cholesterol	5.1 mmol/l
HDL cholesterol	1.0 mmol/l
LDL cholesterol	2.9 mmol/l
Triglyceride	1.7 mmol/l

Urine dip: No protein or blood

She has no family history of note and her body mass index is 20.5 kg/m^2.

What is the most appropriate management with regards to lipid modification?

Start atorvastatin 10mg on	4%
Start atorvastatin 20mg on	25%
Start atorvastatin 40mg on	5%
Perform a QRISK2 assessment	32%
[✓ Reassure her that lipid modification therapy is not required at this stage]	34%

NICE specifically state that we should not use QRISK2 for type 1 diabetics. Instead, the following criteria are used:

- older than 40 years, or

- have had diabetes for more than 10 years or
- have established nephropathy or
- have other CVD risk factors

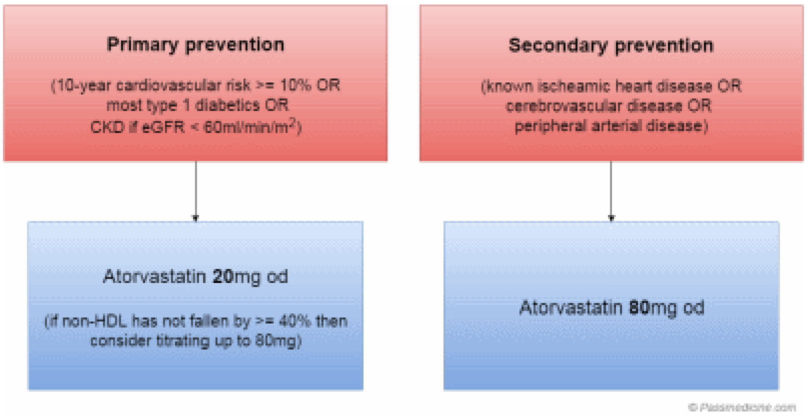
None of these apply in this case.

👍 👎 Discuss (8) Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria

- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:
- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:
- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
    - older than 40 years, or
    - have had diabetes for more than 10 years or
    - have established nephropathy or
    - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake

- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation

- smokers should be encouraged to quit

Next question

Textbooks

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Question 15 of 414 ✗

A patient with type 2 diabetes mellitus is started on sitagliptin. What is the mechanism of action of sitagliptin?

	Incretin inhibitor	3%
🟩	Dipeptidyl peptidase-4 (DPP-4) inhibitor	85%
	Alpha-glucosidase inhibitor	1%
🟥	Glucagon inhibitor	1%
	Glucagon-like peptide-1 (GLP-1) mimetic	10%

Gliptins (DPP-4 inhibitors) reduce the peripheral breakdown of incretins such as GLP-1

Important for me Less important

The correct answer is **Dipeptidyl peptidase-4 (DPP-4) inhibitor**. Sitagliptin works by inhibiting the enzyme dipeptidyl peptidase-4. This enzyme usually breaks down incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are involved in regulating blood glucose levels. By inhibiting DPP-4, sitagliptin increases the levels of these incretin hormones, leading to increased insulin secretion, decreased glucagon release and therefore lower blood glucose levels.

The option **Incretin inhibitor** is incorrect because sitagliptin does not inhibit incretins. Instead, it prevents their degradation and prolongs their action. Incretins are hormones that stimulate a decrease in blood glucose levels.

Alpha-glucosidase inhibitor is also incorrect as this is not how sitagliptin works. Alpha-glucosidase inhibitors such as acarbose work by delaying the digestion of carbohydrates in the small intestine, thereby reducing postprandial hyperglycaemia.

The option **Glucagon inhibitor** is misleading. While it's true that an effect of sitagliptin's mechanism of action results in decreased glucagon release from pancreatic alpha cells, this is secondary to its primary function as a DPP-4 inhibitor and not a direct inhibition of glucagon.

Finally, sitagliptin doesn't act as a **glucagon-like peptide-1 (GLP-1) mimetic**. GLP-1 mimetics or agonists like exenatide and liraglutide mimic the effects of GLP-1 by binding to its receptors on pancreatic beta cells to stimulate insulin secretion. Sitagliptin instead increases endogenous GLP-1 concentration by preventing its breakdown.

👍 👎 Discuss (4) Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
>
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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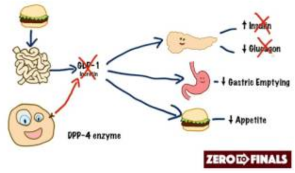
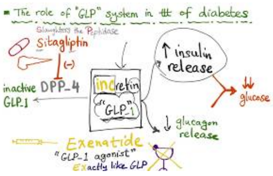
Media


GLP-1
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

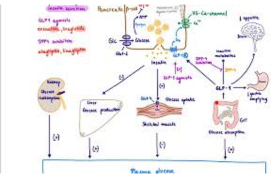
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2


The role of "GLP" system in tt of diabetes
Sitagliptin
(-)
inactive GLP-1
DPP-4
incretin
"GLP-1"
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube

← Question 16 of 414 ✗ ⚐ →

A 37-year-old woman presents to her GP with a six-week history of increasing fatigue, headaches, and cold intolerance. She also reports vomiting and abdominal pain.

Her blood pressure is measured at 95/57 mmHg.

Blood tests are conducted with the following results:

Na^+	129 mmol/L	(135 - 145)
K^+	4.8 mmol/L	(3.5 - 5.0)
Bicarbonate	28 mmol/L	(22 - 29)
Urea	6.0 mmol/L	(2.0 - 7.0)
Creatinine	89 µmol/L	(55 - 120)

Thyroid-stimulating hormone (TSH)	2.1 mU/L	(0.5-5.5)
Free thyroxine (T4)	5.8 pmol/L	(9.0 - 18)

Prolactin	41 ng/mL	(< 20 ng/mL)

What is the definitive treatment for this patient's condition?

	Cabergoline	9%
	Hydrocortisone and fludrocortisone	17%
	Levothyroxine	5%
🟥	Phenoxybenzamine	1%
🟩	Transsphenoidal surgery	68%

Non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - transsphenoidal surgery is therefore the first-line treatment

Important for me Less important

Non-functional adenomas may manifest with pan-hypopituitarism due to the compression of the normally functioning pituitary tissue. The patient in this case has exhibited symptoms indicative of hypothyroidism, such as fatigue and cold intolerance, as well as symptoms consistent with adrenal insufficiency, including hypotension, vomiting and abdominal pain. Additionally, she reports headaches, which could be attributable to dural irritation caused by the growing adenoma. Examination of the blood test results reveals that the patient is experiencing secondary hypothyroidism; this is evidenced by low T4 levels and an inappropriately normal TSH level, indicating a likely pituitary origin of pathology. Furthermore, hyponatraemia is present, supporting the diagnosis of adrenal insufficiency due to diminished ACTH secretion from the pituitary. Hyponatraemia is seen in adrenal insufficiency due to reduced mineralocorticoid production. Non-functioning adenomas can also lead to elevated prolactin levels through stalk effect compression, as observed in this case. The definitive treatment for a non-functioning pituitary adenoma is **transsphenoidal surgery**.

Cabergoline is utilised in the management of prolactinomas. Prolactinomas can induce hypopituitarism through compression of healthy pituitary tissue when they grow to a significant size. However, in this case, the prolactin level is only mildly raised, which is more in keeping with stalk compression. Typically, a prolactinoma would cause a prolactin level > 100ng/mL and a level of 41 ng/mL is more in keeping with a non-functioning adenoma.

Hydrocortisone and fludrocortisone are administered to address adrenal insufficiency conditions such as Addison's disease. These medications might be used as interim measures while awaiting definitive transsphenoidal surgery.

Levothyroxine serves as a therapeutic agent for hypothyroidism arising from conditions such as Hashimoto's disease. In this instance, the laboratory findings point to a secondary cause for her hypothyroidism. When coupled with adrenal insufficiency, it strongly indicates the presence of a non-functioning pituitary adenoma, warranting surgical intervention.

Phenoxybenzamine, an alpha-adrenergic receptor antagonist, is employed preoperatively to manage hypertension associated with pheochromocytomas. While such tumours often cause headaches similar to those reported by our patient, they are typically accompanied by palpitations and sweating—symptoms absent in this case—and are not linked with secondary hypothyroidism or adrenal insufficiency.

👍 👎 Discuss (1) Improve

Next question

Pituitary adenoma ★

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:
- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)
- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
    - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:
- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:
- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of

- medical therapy:
    - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
    - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas
    - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery
    - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
    - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
    - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
    - indicated for residual or recurrent tumours post-surgery

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Patient.info 👍 7 👎 0

Pituitary tumours review

Report broken link

PassMedicine

Question 17 of 414 ✓

A 42-year-old woman is reviewed in the general medical clinic with a history of abdominal cramping and fatigue. She reports a reduced passage of stools, only passing one hard stool every other day.

Blood tests were taken at the clinic:

Hb	165 g/L	Male: (135-180) Female: (115 - 160)
Platelets	200 * 10^9/L	(150 - 400)
WBC	5.6 * 10^9/L	(4.0 - 11.0)

Na^+	147 mmol/L	(135 - 145)
K^+	4.9 mmol/L	(3.5 - 5.0)
Urea	8.0 mmol/L	(2.0 - 7.0)
Creatinine	119 µmol/L	(55 - 120)

Calcium	2.90 mmol/L	(2.1-2.6)
Phosphate	0.55 mmol/L	(0.8-1.4)
Parathyroid hormone (PTH)	70 pg/mL	(10-55pg/mL)
Thyroid stimulating hormone (TSH)	5.6 mU/L	(0.5-5.5)
Free thyroxine (T4)	8.7 pmol/L	(9.0 - 18)

What is the next most appropriate management for this patient?

Bisphosphonates	12%
Cinacalcet	13%
Levothyroxine	7%
[✓ Referral for surgery]	64%
Monitor and repeat biochemistry tests in 4 weeks	5%

The definitive management of primary hyperparathyroidism is total parathyroidectomy

Important for me Less important

Referral for surgery is the correct answer. The patient here presents with symptomatic hypercalcemia secondary to primary hyperparathyroidism. The biochemistry tests show a raised parathyroid hormone level (PTH) with inappropriately elevated calcium and phosphate, which indicates that the problem is occurring at the level of the parathyroid glands. The NICE guidelines (NG 132) state that all patients with symptomatic hyperparathyroidism or with an adjusted calcium level above 2.85 mmol/mL should be referred to a surgeon with expertise in parathyroid surgery in the first instance.

Bisphosphonates can be considered in patients with primary hyperparathyroidism who are at risk of fragility fractures. However, they are not indicated in the treatment of chronic hypercalcemia in the context of primary hyperparathyroidism. There is no mention of an increased risk of fractures in this instance, and the patient should be referred to the surgical team to address the cause of the hypercalcemia.

Cinacalcet can be considered as a non-surgical option in primary hyperparathyroidism for patients where surgery is contraindicated or surgical management has been unsuccessful. Cinacalcet should be offered for non-surgical management in asymptomatic patients with an adjusted calcium level above 3.0 mmol/mL and symptomatic patients with an adjusted calcium level above 2.85mmol/mL. In the scenario presented there are no contraindications to surgery mentioned and so surgery should be considered in the first instance.

Levothyroxine is incorrect as, whilst the patient has a mildly deranged thyroid function, this would not necessitate starting treatment. The most important diagnosis here is primary hyperparathyroidism. When presented with these results for thyroid function, the best management option would be to repeat these results in 4-6 weeks and monitor for any further deterioration in thyroid function.

Repeating biochemistry in 4 weeks is incorrect as the patient can be diagnosed with primary hyperparathyroidism from the results presented at this visit. There is no need to delay the referral to the surgical team. If there is any ambiguity with results it is sometimes an option to repeat the blood tests in a few weeks to be more confident about a diagnosis.

👍 👎 💬 Discuss (8) Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':
- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations
- bloods
  - raised calcium, low phosphate
  - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
  - pepperpot skull
  - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor

Next question

Textbooks

High-yield textbook

Extended textbook

Media

Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2

Parathyroid Glands and Hyperparathyroidism

PassMedicine

Question 18 of 414 ✗

A 29-year-old female who is 7 weeks into her first pregnancy is investigated for excessive sweating and tremor. Blood tests reveal the following:

TSH	< 0.05 mu/l
T4	188 nmol/l

What is the most appropriate management?

Immediate surgery	3%
🟥 Carbimazole	17%
Surgery at start of third trimester	1%
🟩 Propylthiouracil	78%
Radioiodine	1%

According to CKS:

> *Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole, as propylthiouracil has been associated with a small risk of severe hepatic injury.*

Discuss (2) Improve

Next question

Pregnancy: thyroid problems ★

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points
- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

PassMedicine

Question 19 of 414 ✗

A 45-year-old woman with a history of type 1 diabetes and Grave's disease attends the emergency department unwell. She reports not having taken any of her medications for several days, as she has been drinking heavily. She has not been taking illicit drugs. On examination, she is agitated and flushed, with observations as follows:

- Heart rate - 110bpm irregular
- Blood pressure - 160/105 mmHg
- Respiratory rate - 32/min and deep
- Temperature - 39.4°C
- Saturations - 99% on air

Her blood sugars return as 'HIGH', and blood ketones are elevated at 3.5mmol/L. You initiate treatment for diabetic ketoacidosis with fluids and fixed-rate insulin.

What other treatment is required?

	Broad spectrum antibiotics	10%
🟥	Carbimazole, hydrocortisone, propranolol	38%
	Cyproheptadine	1%
	Dantrolene	2%
🟩	Hydrocortisone, propranolol, propylthiouracil	49%

Thyrotoxic storm is treated with beta blockers, propylthiouracil and hydrocortisone

Important for me Less important

Hydrocortisone, propranolol, propylthiouracil is the treatment of choice for a thyroid storm, which is what this patient has developed. This is a medical emergency with a mortality rate of >10%, and normally occurs in patients with known hyperthyroidism who undergo a trigger (e.g. thyroid surgery, sepsis, DKA). Hydrocortisone acts to prevent the peripheral conversion of T4 to T3 and is particularly effective in Graves' disease. Propranolol blocks the effects of thyroid hormones and reduces the heart rate. Propylthiouracil stops the release and production of thyroid hormones and reduces the peripheral conversion of T4 to T3.

Carbimazole, hydrocortisone, propranolol is incorrect. Propylthiouracil is preferred to carbamazepine because the latter will only prevent the release of thyroid hormones, and will not prevent the conversion of T4 to T4 peripherally.

Broad spectrum antibiotics would be the correct answer in sepsis. While this can cause tachycardia and fever, in the context of a patient with Grave's disease who is undergoing a triggering event and has not been taking her medication, a thyroid storm must be considered.

Cyproheptadine is the treatment of choice in serotonin syndrome. This condition is generally seen in patients on SSRIs and those taking serotoninergic drugs, such as ecstasy. While this can present with flushing, tachycardia, hyperthermia, and agitation, it is unlikely in this patient who has no reason to be taking SSRIs and who has not been taking illicit medications.

Dantrolene is the treatment for neuroleptic malignant syndrome, a condition caused by antipsychotics, dopaminergic/antidopaminergic drugs, and tranquilisers. Given that this patient is not known to be on any of these medications, this is not the correct answer.

Discuss (10) Improve

Next question

Thyroid storm

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating events:
- thyroid or non-thyroidal surgery
- trauma
- infection
- acute iodine load e.g. CT contrast media

Clinical features include:
- fever > 38.5ºC
- tachycardia
- confusion and agitation
- nausea and vomiting

- hypertension
- heart failure
- abnormal liver function test - jaundice may be seen clinically

Management:

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- beta-blockers: typically IV propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

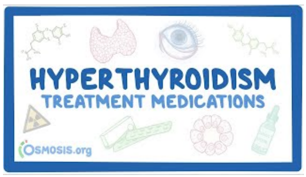
Next question

Textbooks

High-yield textbook

Extended textbook

Media


HYPERTHYROIDISM
TREATMENT MEDICATIONS
Osmosis.org

Hyperthyroidism treatment medications

Osmosis - YouTube 👍 5 👎 0

THYROID
STORM

PassMedicine

Question 20 of 414 ✓

A 28-year-old woman presents to her general practitioner for a routine pregnancy review. She is currently 26 weeks pregnant and so far has not experienced any complications or issues. A fasting glucose test is performed:

Fasting glucose	6.8 mmol/L	(<5.6)

She is commenced on metformin. Two weeks later, the fasting glucose test is repeated:

Fasting glucose	6.2 mmol/L	(<5.6)

What is the most appropriate next step in management?

Add glibenclamide	1%
Add gliclazide	2%
[✓ Add insulin]	75%
Continue metformin and repeat the test in two weeks	12%
Perform a 2-hour oral glucose tolerance test (OGTT)	9%

In gestational diabetes, if blood glucose targets are not met with diet/metformin then insulin should be added

Important for me Less important

Gestational diabetes mellitus (GDM) is diagnosed when fasting glucose is at least 5.6 mmol/L, or 2-hour glucose is at least 7.8 mmol/L. After an initial trial of dietary/exercise modification, metformin is started if glucose targets are not met within 1-2 weeks. Following this, if targets are still not met - as is the case here - the next step is to **add insulin**. If the initial fasting glucose was 7 mmol/L or greater, insulin would typically be commenced straight away.

Glibenclamide may be offered to women with GDM who do not tolerate metformin, or to those who subsequently decline insulin treatment. It should not be offered here, as insulin should be offered first.

Gliclazide is commonly used in DM management if metformin alone is ineffective. It is typically used in DM in non-pregnant patients, not in GDM.

Simply **continuing metformin and repeating the test in two weeks** is inappropriate. Guidelines state that, if the target has not been met after 1-2 weeks of metformin use, insulin should be added.

The fasting glucose values measured here are sufficient to guide further management. **Performing a 2-hour OGTT** is unnecessary in this instance and would not alter the next step in management, which is to commence insulin.

👍 👎 Discuss (1) Improve

Next question

Gestational diabetes ★

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:
- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes
- BMI of > 30 kg/m^2
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes
- the oral glucose tolerance test (OGTT) is the test of choice

- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

NICE 👍 3 👎 5

2015 Management of diabetes in pregnancy

Report broken link

Media

PassMedicine

Question 21 of 414 ✓

A 62-year-old HGV driver is reviewed. He was diagnosed last year with type 2 diabetes mellitus. Following weight loss and metformin his HbA1c has decreased from 74 mmol/mol (8.9%) to 68 mmol/mol (8.4%). What is the most suitable next step in management?

Add exenatide	20%
Make no changes to management	15%
Add gliclazide	29%
Stop metformin for a period to ensure hypoglycaemic awareness is not lost	2%
Add pioglitazone	34%

Pioglitazone is the best option here as it would not put him at risk of hypoglycaemia, which obviously could be dangerous given his job. The NICE guidelines would also support the use of a DPP-4 inhibitor (e.g. sitagliptin or vildagliptin) in this situation.

Discuss (17) Improve

Next question

Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

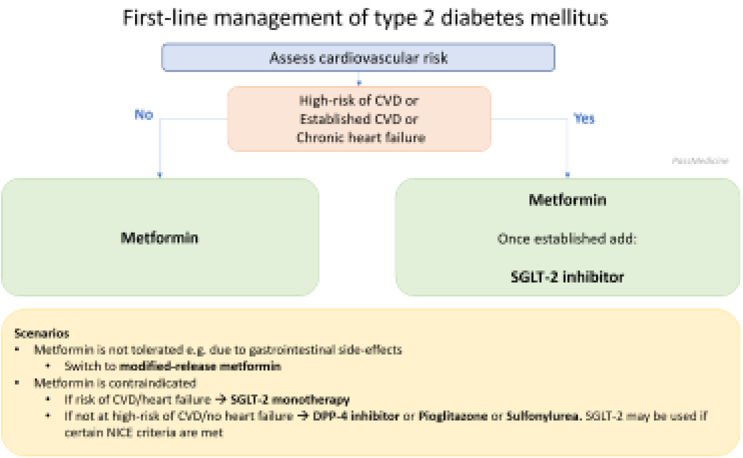
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	**HbA1c target**
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
Metformin
Metformin
Once established add:
SGLT-2 inhibitor
Scenarios
Metformin is not tolerated e.g. due to gastrointestinal side-effects
Switch to modified-release metformin
Metformin is contraindicated
If risk of CVD/heart failure → SGLT-2 monotherapy
If not at high-risk of CVD/no heart failure → DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors

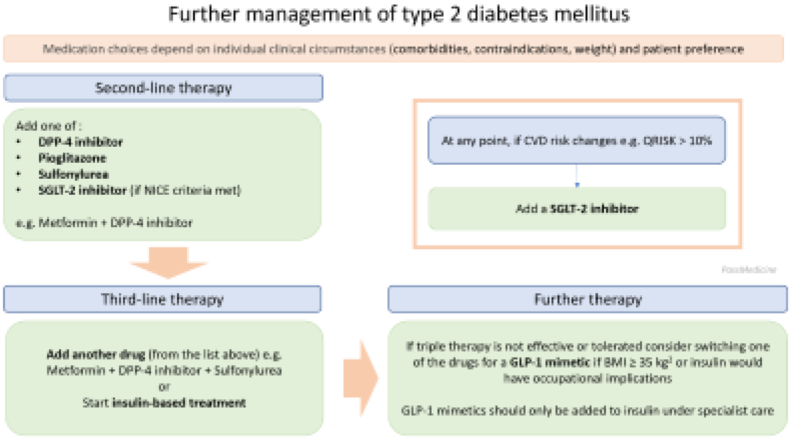
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:

  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
• DPP-4 inhibitor
• Pioglitazone
• Sulfonylurea
• SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:
- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:
- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

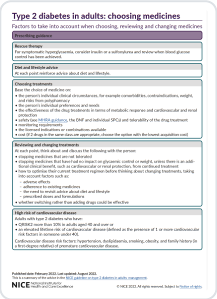
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

Published date: February 2022. Last updated: August 2022.
This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

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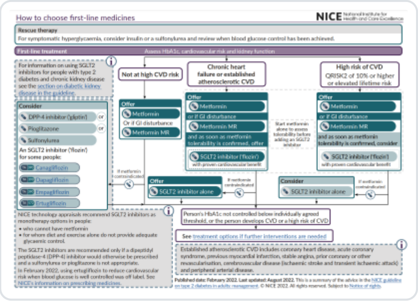

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk

Offer
- Metformin
Or if GI disturbance
- Metformin MR

Chronic heart failure or established atherosclerotic CVD

Offer
- Metformin
or if GI disturbance
- Metformin MR
and as soon as metformin tolerability is confirmed, offer
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk

Offer
- Metformin
or if GI disturbance
- Metformin MR
and as soon as metformin tolerability is confirmed, consider
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Consider
- DPP-4 inhibitor ('gliptin') or
- Pioglitazone or
- Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin

If metformin contraindicated

Offer
- SGLT2 inhibitor alone

If metformin contraindicated

Consider
- SGLT2 inhibitor alone

If metformin contraindicated

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:
- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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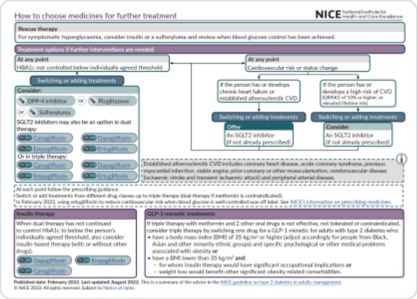
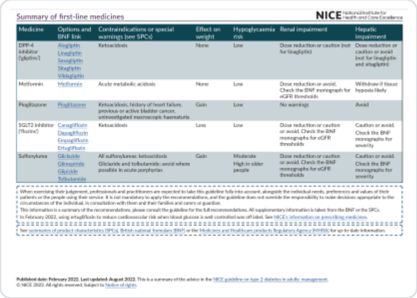
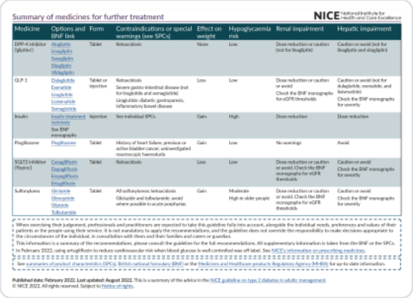






Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

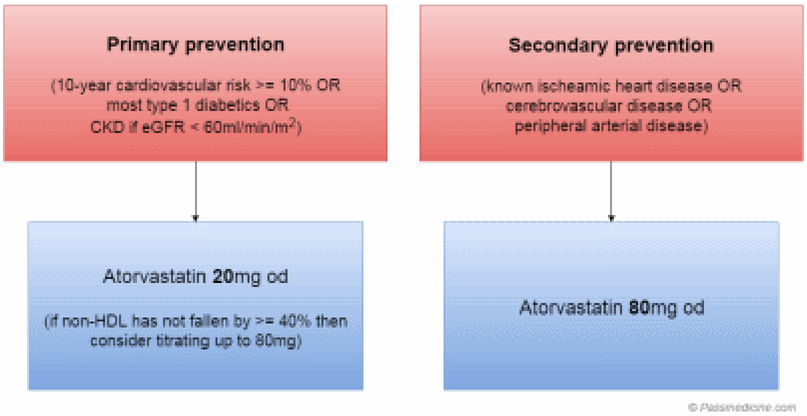
	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischaemic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 3 0

2014 Lipid modification guidelines

7 minute medics 11 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

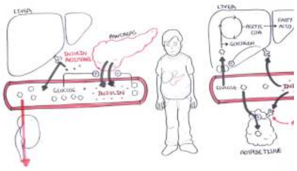
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media

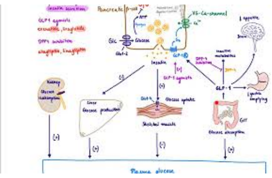


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

Report broken media

Score: **42.9%**

Question 22 of 414 ✗

In patients with suspected insulinoma, which one of the following is considered the best investigation?

🟥 Oral glucose tolerance test	4%
Insulin tolerance test	3%
Early morning C-peptide levels	28%
Glucagon stimulation test	5%
🟩 Supervised fasting	60%

Insulinoma is diagnosed with supervised prolonged fasting

Important for me Less important

The correct answer is **Supervised fasting**. Insulinomas are pancreatic tumours that produce excessive amounts of insulin, leading to hypoglycaemia. The diagnosis of insulinoma is typically based on demonstrating inappropriately high insulin levels during a period of hypoglycaemia. This is best achieved through supervised fasting, which can last up to 72 hours under medical supervision. During this time, blood glucose and insulin levels are measured regularly. The test is terminated when blood glucose drops below 2.2 mmol/L or if the patient develops symptoms of hypoglycaemia.

The option **Oral glucose tolerance test** isn't the best investigation for suspected insulinoma. This test measures how well your body handles a standard amount of glucose and it's typically used to diagnose diabetes or prediabetes, not insulinomas.

Insulin tolerance test involves injecting insulin into a patient and measuring how long it takes for their blood sugar to drop. This test is primarily used in diagnosing adrenal insufficiency or growth hormone deficiency rather than an insulinoma.

Early morning C-peptide levels can be useful in differentiating endogenous from exogenous hyperinsulinaemia as C-peptide is co-secreted with insulin by the pancreas but does not exist in synthetic forms of insulin. However, this would not be the first-line investigation for suspected insulinoma as it doesn't provide information about inappropriate secretion relative to blood glucose levels.

Lastly, **Glucagon stimulation test**, while useful in some contexts such as assessing for growth hormone deficiency or adrenal insufficiency, does not have a role in diagnosing an insulinoma because glucagon stimulates glycogenolysis and gluconeogenesis thereby increasing blood glucose levels which could mask the hypoglycaemic effect caused by an insulinoma.

Discuss (4) Improve

Next question

Insulinoma ★

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics
- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

Features
- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis
- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Management
- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

Next question

PassMedicine

Question 23 of 414 ✗

A 30-year-old woman presents to the emergency department with a several-month history of headaches and reports a six-month history of weight gain accompanied by cold intolerance.

Her vital signs are within normal limits. The laboratory results are as follows:

TSH	10.0 mIU/L	0.4-4.0
FT4	0.5 pmol/L	12 – 21.9
FSH	6.0 IU/L	10-90
LH	60 IU/L	75-150
Prolactin	60 ng/ml	< 25

What is the most likely diagnosis?

	Hypogonadism	0%
🟥	Hypothyroidism	13%
🟩	Non functioning pituitary adenoma	69%
	Polycystic ovarian syndrome	0%
	Prolactinoma	18%

The presence of an elevated prolactin level along with secondary hypothyroidism and hypogonadism is indicative of stalk compression is consistent with a non-functioning pituitary adenoma

Important for me Less important

The correct diagnosis, in this case, is a **non-functioning pituitary adenoma**, as evidenced by the patient's symptoms of headache and the presence of secondary hypothyroidism, along with decreased levels of FSH and LH, which suggest hypogonadism.

Hypothyroidism on its own does not account for the full clinical picture. While it may coexist with a non-functioning pituitary adenoma, the constellation of symptoms more strongly suggests that a non-functioning pituitary adenoma is the primary pathology.

A diagnosis of **polycystic ovarian syndrome (PCOS)** does not align with the clinical findings; PCOS typically presents with increased levels of LH and FSH, as well as hirsutism—symptoms that are absent in this patient.

Considering the patient also has secondary hypothyroidism, pure **hypogonadism** is an unlikely diagnosis. The combination of findings makes a non-functioning pituitary adenoma more plausible.

Furthermore, a **prolactinoma** is inconsistent with the observed clinical features. The combination of secondary hypothyroidism and hypogonadism more convincingly indicates a non-functioning pituitary adenoma as the underlying condition.

👍 👎 Discuss Improve

Next question

Pituitary adenoma ★

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:
- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)
- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
  - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)

- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:

- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:

- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of

- medical therapy:
  - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
  - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas
  - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery
  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

PassMedicine

← Question 24 of 414 ✗ ⚐ →

Which one of the following statements regarding maturity-onset diabetes of the young (MODY) is true?

🟩	There is usually a strong family history	76%
🟥	Body mass index is typically > 30	5%
	Doesn't respond to glimepiride	4%
	Autosomal recessive inheritance	10%
	Frequent episodes of diabetic ketoacidosis are typical	6%

The correct answer is **There is usually a strong family history**. Maturity-onset diabetes of the young (MODY) is a group of monogenic forms of diabetes that typically presents in adolescence or early adulthood. It is characterised by autosomal dominant inheritance, hence a strong family history is often present. This means that an affected individual has a 50% chance of passing the condition on to each offspring.

The statement **Body mass index is typically > 30** is incorrect. MODY patients are typically non-obese and have normal or low body mass index (BMI). This distinguishes MODY from type 2 diabetes, where BMI is often greater than 25-30 due to insulin resistance.

Doesn't respond to glimepiride is also incorrect. Glimepiride, a sulfonylurea, stimulates insulin secretion from pancreatic beta cells and can be effective in some types of MODY, particularly MODY 2 and MODY 3 where there's functional impairment of these cells. However, response to glimepiride may vary depending on the specific genetic mutation present in different subtypes of MODY.

Regarding the statement **Autosomal recessive inheritance**, this too is incorrect as it contradicts the actual inheritance pattern for MODY which is autosomal dominant. Autosomal recessive diseases require both parents to carry and pass on the faulty gene for the disease to manifest in their offspring.

Lastly, **Frequent episodes of diabetic ketoacidosis are typical** does not accurately describe clinical features associated with MODY. Diabetic ketoacidosis (DKA) tends to occur more frequently in patients with type 1 diabetes due to absolute insulin deficiency. In contrast, individuals with MODY generally have some endogenous insulin production preventing DKA under most circumstances.

Discuss (2) Improve

Next question

MODY

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

Textbooks

High-yield textbook

Extended textbook

PassMedicine

Question 25 of 414 ✗

A 55-year-old woman presents to the emergency department with complaints of persistent fatigue, headache, and occasional blurred vision that have developed over several months.

She has normal vital signs but reports experiencing weight gain and cold intolerance. On examination of her visual fields, she is found to have peripheral vision loss. Her blood test results are as follows:

TSH	15.0 mIU/L	0.4-4.0
FT4	0.05 pmol/L	12 – 21.9
FSH	30 IU/L	40-250
LH	20 IU/L	30-200
Prolactin	500 ng/ml	< 25

What is the first-line treatment for the most likely diagnosis?

Bromocriptine	15%
Cabergoline	5%
Octreotide	3%
Radiotherapy	5%
Surgery	72%

Non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - transsphenoidal surgery is therefore the first-line treatment

Important for me Less important

The correct choice in this scenario is **surgical resection**, which represents the first-line management for this patient. The clinical presentation and laboratory findings are indicative of a non-functioning pituitary macroadenoma. Symptoms such as fatigue, weight gain, and cold intolerance may be attributed to secondary hypothyroidism, characterised by an elevated TSH and low FT4 levels, resulting from tumour compression on the normal pituitary gland. Additionally, headache and visual field defects—specifically bitemporal hemianopia—are frequently associated with a pituitary macroadenoma due to the expansive effect of the lesion on the optic chiasm.

Bromocriptine is not an appropriate selection because it acts as a dopamine agonist primarily indicated for prolactin-secreting adenomas (prolactinomas). Given that the patient exhibits signs of secondary hypothyroidism alongside headache and bitemporal hemianopia, these symptoms do not align with those typically observed in prolactinoma but rather suggest a non-functioning pituitary macroadenoma.

Similarly, **cabergoline** is another dopamine agonist utilised predominantly for treating prolactinomas; hence it is not suited for cases of non-functioning pituitary macroadenoma. The patient's clinical manifestation and laboratory evidence of secondary hypothyroidism combined with visual field impairment support the diagnosis of non-functioning pituitary macroadenoma.

Octreotide has its use in managing growth hormone-secreting adenomas. As such, given that the clinical picture and laboratory results do not correspond to this type of tumour, octreotide would be an incorrect choice for treatment in this context as it holds no therapeutic benefit for non-functioning pituitary macroadenomas.

Finally, while **radiotherapy** might be considered if surgical intervention is contraindicated or if there is residual disease following surgery, it is generally not employed as a primary therapy. Radiotherapy may also be indicated in cases where tumour recurrence occurs after surgery. However, given that the question specifies seeking first-line treatment options, radiotherapy does not represent the correct choice under these circumstances.

👍 👎 Discuss Improve

Next question

Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

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- MRI brain with contrast

Differential diagnoses include:
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- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

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- transsphenoidal surgery

  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Patient.info 👍 7 👎 0

Pituitary tumours review

Report broken link

Score: **36%**

1 ✓
2 ✓
3 ✓

PassMedicine

Question 26 of 414 ✓

A 70-year-old patient is brought to the emergency department. She has a GCS of 11. Her relatives tell you that she has been drinking large amounts of water in order to remain well hydrated during the hot weather. You find that she has a sodium level of 108 mmol/l. Her most recent sodium was 131 mmol/l when last checked 3 weeks ago. What is the underlying pathology by which acute hyponatraemia is causing her reduced GCS?

Central pontine myelinolysis	23%
Concurrent hypoglycaemia	1%
Intracranial haemorrhage	2%
Cerebral oedema	72%
Cerebral vasospasm	2%

Acute severe hyponatraemia can cause cerebral oedema

Important for me Less important

The correct answer is cerebral oedema. The patient has acute hyponatraemia, most likely as a result of water intoxication in this scenario. Acute hyponatraemia causes cerebral oedema by reducing plasma osmolality, which causes water to move out of the plasma into the brain cells down the osmotic gradient. Cerebral oedema causes drowsiness and seizures.

Central pontine myelinolysis can occur if hyponatraemia is corrected too rapidly. The other mechanisms are not classically involved in hyponatraemia.

Effects of hyponatraemia on the brain
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470176/

Discuss (2) Improve

Next question

Hyponatraemia: treatment ★

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:

- duration of hyponatremia: is it acute or chronic?
    - acute: develops over a period of < 48 hours
    - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
    - mild: 130-134 mmol/L
    - moderate: 120-129 mmol/L
    - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
    - patients with mild hyponatraemia may be symptomatic
    - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
    - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
    - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
    - euvolemic hyponatraemia: SIADH
    - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected

- normal, i.e. isotonic, saline (0.9% NaCl)

- this may sometimes be given as a trial
  - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
  - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider medications:
  - demeclocycline
  - vaptans (see below)

If a hypervolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):

- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia
- pathophysiology:

  - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
  - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 15 👎 3

2017 Hyponatraemia â€“ presentations and management

Report broken link

PassMedicine

Question 27 of 414 ✗

Which one of the following statements regarding the normal menstrual cycle is **incorrect**?

	A number of follicles develop in the follicular phase under the influence of FSH	6%
	The luteal phase is also known as the secretory phase	7%
🟥	The follicular phase follows menstruation and occurs around day 5 - 13	10%
🟩	A surge of FSH causes ovulation	67%
	Progesterone levels are low in the follicular phase	11%

LH surge causes ovulation

Important for me Less important

The **incorrect** statement regarding the normal menstrual cycle is '**A surge of FSH causes ovulation**'. In fact, it is a surge of luteinising hormone (LH), not follicle-stimulating hormone (FSH), that triggers ovulation. The LH surge occurs in response to rising levels of oestrogens produced by the maturing follicle, leading to the release of an egg from the dominant follicle around day 14 of a typical 28-day menstrual cycle.

Discussing each of the other options:

'**A number of follicles develop in the follicular phase under the influence of FSH**' is correct. During the early and mid-follicular phase, FSH stimulates the growth and maturation of several ovarian follicles. However, only one typically becomes dominant and proceeds to full maturity.

'**The luteal phase is also known as the secretory phase**' is also correct. Following ovulation, during this phase, the corpus luteum secretes progesterone which prepares the endometrium for the potential implantation of a fertilised egg.

'**The follicular phase follows menstruation and occurs around day 5 - 13**' is a true statement. The initial part of the menstrual cycle after menstruation indeed involves the recruitment and development of multiple ovarian follicles during what's called 'the follicular phase'. This usually lasts until about day 13 or 14 in a typical 28-day cycle.

Finally, '**Progesterone levels are low in the follicular phase**' is also accurate. Progesterone secretion primarily occurs after ovulation during the luteal or secretory phase to prepare for possible pregnancy. Prior to ovulation, during the follicular phase, progesterone levels remain relatively low.

Discuss (2) Improve

Next question

Menstrual cycle ★

The menstrual cycle may be divided into the following phases:

	Days
Menstruation	1-4
Follicular phase (proliferative phase)	5-13
Ovulation	14
Luteal phase (secretory phase)	15-28

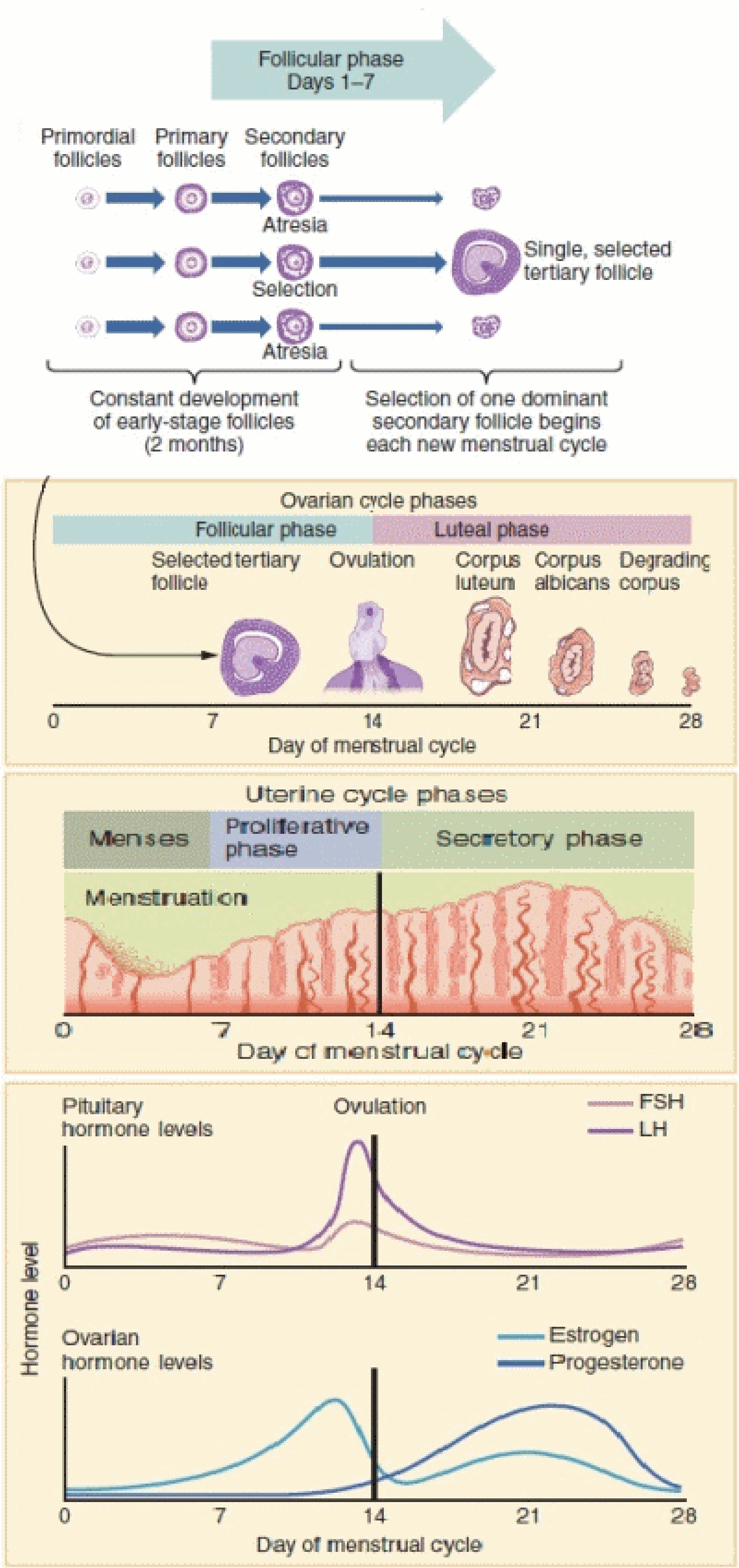

Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Single, selected tertiary follicle
Selection
Atresia
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle
Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle
Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle
Pituitary hormone levels
Ovulation
FSH
LH
0
7
14
21
28
Hormone level
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

Image sourced from Wikipedia

Further details are given in the table below

	Follicular phase (proliferative phase)	Luteal phase (secretory phase)
Ovarian histology	A number of follicles develop. One follicle will become dominant around the mid-follicular phase	Corpus luteum
Endometrial histology	Proliferation of endometrium	Endometrium changes to secretory lining under influence of progesterone
Hormones	A rise in FSH results in the development of follicles which in turn secrete oestradiol When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation	Progesterone secreted by corpus luteum rises through the luteal phase. If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall Oestradiol levels also rise again during the luteal phase
Cervical mucus	Following menstruation the mucus is thick and forms a plug across the external os Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit	Under the influence of progesterone it becomes thick, scant, and tacky
Basal body temperature	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels

Next question

Textbooks

High-yield textbook

Extended textbook

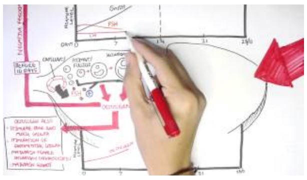
Links

Wikipedia 👍 2 👎 1

Menstrual cycle (including diagram)

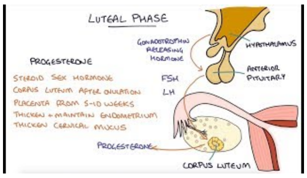
Report broken link

Media



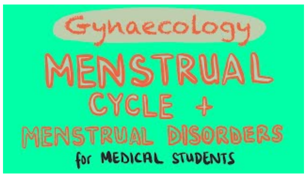
Female Reproductive System - Menstrual Cycle, Hormones and Regulation

Armando Hasudungan - YouTube 👍 21 👎 1


LUTEAL PHASE
GONADOTROPHIN RELEASING HORMONE
HYPOTHALAMUS
PROGESTERONE
STEROID SEX HORMONE
CORPUS LUTEUM AFTER OVULATION
PLACENTA FROM 8-10 WEEKS
THICKEN + MAINTAIN ENDOMETRIUM
THICKEN CERVICAL MUCUS
FSH
LH
ANTERIOR PITUITARY
PROGESTERONE
CORPUS LUTEUM

Understanding the Menstrual Cycle

Zero to Finals - YouTube 👍 8 👎 1


Gynaecology
MENSTRUAL
CYCLE +
MENSTRUAL DISORDERS
for MEDICAL STUDENTS

Menstrual Cycle + Menstrual Disorders For Medical Students

MedFlix - YouTube 👍 4 👎 1

PassMedicine

Question 28 of 414 ✗

A 68-year-old woman was admitted to hospital after being found on the floor and confused. The paramedics noted a past medical history of depression and could only find sertraline by her bedside.

On examination, she was found to be dehydrated with a capillary refill time of 3 seconds and a heart rate of 115/min. The rest of her observations showed her blood pressure was 130/50 mmHg, temperature 36.4ºC, saturations of 96% on room air with a respiratory rate of 16/min. She had a normal cardiorespiratory, abdominal, upper and lower limb neurological exam. Her glasgow coma score was 13 (E4 V4 M5) with a normal cranial nerve exam.

Blood results showed:

Creatinine	173 µmol/L	(55 - 120)
Calcium	3.4 mmol/L	(2.1-2.6)
Parathyroid hormone	33 pmol/L	(0 - 6.4)

The rest of her full blood count and biochemistry were normal. Paracetamol and salicylate levels were undetectable. CT brain showed no acute pathology.

She was treated for hypercalcaemia secondary to primary hyperparathyroidism with intravenous fluids, intravenous zoledronic acid and later required calcitonin. Three weeks into her admission she was catheterised for multiple episodes of incontinence as she was still requiring significant nursing care. Her urine output was 3.3 litres/day. She was haemodynamically stable.

Her latest bloods showed:

Hb	131 g/L	(115 - 160)
Na^+	143 mmol/L	(135 - 145)
K^+	3.4 mmol/L	(3.5 - 5.0)
Urea	7.2 mmol/L	(2.0 - 7.0)
Creatinine	100 µmol/L	(55 - 120)
CRP	5 mg/L	(< 5)
Calcium	2.74 mmol/L	(2.1-2.6)
Blood sugar	6.7 mmol/L	

A water deprivation test was undertaken and showed:

Plasma osmolality after 8 hours	303 mOsm/kg
Urine osmolality after 8 hours	287 mOsm/kg
Urine osmolality 4 hours after desmopressin	289 mOsm/kg

What is the underlying cause for her polyuria?

	Zoledronic acid use	7%
🟩	Hypercalcaemia	43%
🟥	Sertraline use	20%
	Polyuric phase of acute kidney injury (AKI)	25%
	Diabetes	5%

Water deprivation test: nephrogenic DI

- urine osmolality after fluid deprivation: low
- urine osmolality after desmopressin: low

Important for me Less important

This is a case of hypercalcaemia induced nephrogenic diabetes insipidus driven by primary hyperparathyroidism. The clinical course and water deprivation test results both suggest nephrogenic diabetes insipidus. Hypercalcemia is a well-documented cause.

Now to look at the other options.

Zoledronic acid or sertraline are not known drug cause of nephrogenic diabetes insipidus. If the patient had been on lithium, demeclocycline, ofloxacin or orlistat, then it may have been suggestive of it.

Polyuric phase of an AKI- could be plausible if this was during the active recovery phase of the AKI, however at three weeks down the line, it is less likely.

The patient's random blood sugar is 6.7 at the moment and not suggestive of diabetes, particularly if this polyuria is new and not an issue prior to admission. A formal HbA1c and a urine dip could be done to completely exclude it, but the clinical suspicion is not high from the history.

This patient should go on to have an inpatient parathyroidectomy as she is suffering from severe symptoms that prevent outpatient care.

Discuss (7) Improve

Next question

Water deprivation test ★

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

PassMedicine

Question 29 of 414 ✗

A 31-year-old woman presents for review in the outpatients' department. She has a past medical history of polycystic ovarian syndrome and has been unsuccessfully attempting to conceive for the past ten months.

Upon examination she is hirsute. Height and weight measurements are taken, confirming a body mass index (BMI) of 24kg/m^2.

What is the most appropriate management option for this patient?

🟩	Clomifene	72%
	Goserelin	3%
	In vitro fertilisation (IVF)	1%
🟥	Metformin	16%
	Weight loss	7%

Infertility in PCOS - clomifene is typically used first-line

Important for me Less important

The correct answer is **clomifene**. This patient is experiencing subfertility - a common consequence of polycystic ovarian syndrome (PCOS). In the absence of contraindications, clomifene tends to be used as a first-line treatment for fertility issues in the context of PCOS. Compared to other treatments for anovulation such as gonadotropins, clomifene has a lower risk of inducing ovarian hyperstimulation syndrome.

Goserelin is incorrect. Goserelin is a gonadotropin-releasing hormone agonist used in the treatment of hormone-sensitive prostate cancer. Polycystic ovarian disease is listed in the BNF as a caution when prescribing goserelin, as, upon commencement of treatment, levels of luteinizing hormone are likely to rise even higher.

In vitro fertilisation (IVF) is incorrect. Women aged under 40 are typically not offered IVF for infertility until they have been trying to conceive for a total of two years. Although there may be some flexibility in the approval criteria for women with endocrine conditions such as PCOS, it would be more appropriate to try medical optimisation of fertility with agents such as clomifene before referral for IVF.

Metformin is incorrect. Although metformin may have a role in the promotion of fertility in patients with PCOS who are obese, for this patient, who has a normal BMI, metformin as monotherapy is an inferior option to clomifene.

Weight loss is incorrect. This patient has a BMI within the normal range. It is unlikely that her weight is contributing significantly to her subfertility, and she should be offered pharmacological therapy with clomifene rather than lifestyle advice alone.

Discuss (1) Improve

Next question

Polycystic ovarian syndrome: management

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

General
- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne
- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility
- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be

used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

Next question

Textbooks

High-yield textbook

Extended textbook

Links

RCOG 👍 4 👎 0

Opinion paper on metformin in PCOS

ESHRE (European Society of Human Reproduction and Embryology) 👍 1 👎 0

2018 International Evidence Based Guideline for the Assessment and Management of PCOS

Patient.info 👍 1 👎 0

Question 30 of 414 ✗

A 19-year-old is brought into the emergency department with reduced consciousness. He is a known diabetic and his friends report he had been drinking alcohol with them all afternoon before becoming sleepy. They remember him taking his insulin with some food approximately six hours prior.

Observations are as follows
- Temperature 37.7ºC
- Oxygen saturation 96% in air
- Heart rate 89 beats per minute
- Respiratory rate 18 breaths per minute
- Blood pressure 110/60mmHg

You calculate his GCS (Glasgow Coma Scale) as 11 (E2, V4, M5). His blood sugar was 2.4mmol/L.

What mechanism is likely responsible for his presentation?

🟩 Alcohol causing increased insulin secretion	52%
Increased glycogenolysis	13%
🟥 Increased pancreatic exocrine activity	10%
Low carbohydrate content in alcohol decreasing blood sugar levels	16%
Promotion of gluconeogenesis	9%

Alcohol results in exaggerated insulin secretion → hypoglycaemia. The mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion

Important for me Less important

The correct answer is **alcohol causing increased insulin secretion**. This patient has presented with symptoms in keeping with hypoglycaemia, precipitated by alcohol use. Alcohol results in exaggerated insulin secretion causing hypoglycaemia. The mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation leading to a redistribution of pancreatic blood flow from the exocrine into the endocrine parts and thus increased insulin secretion. In a young type 1 diabetic it is thought that the pancreas still retains some of its ability to produce insulin, resulting in higher insulin requirements as the disease progresses.

Increased glycogenolysis is incorrect as alcohol impairs glycogenolysis. Glycogenolysis is the biochemical pathway in which glycogen breaks down into glucose-1-phosphate and glucose.

Increased pancreatic exocrine activity is incorrect. Alcohol causes the redistribution of blood flow from the exocrine part of the pancreas (responsible for the digestion of food) to the endocrine part (responsible for insulin secretion).

Low carbohydrate content in alcohol decreasing blood sugar levels is incorrect. Several alcoholic drinks (such as beers, cider and liqueurs) contain carbohydrates and so may cause blood sugar levels to rise initially but later patients become more susceptible to low blood glucose levels due to exaggerated insulin secretion.

Promotion of gluconeogenesis is incorrect as alcohol actually inhibits gluconeogenesis. Gluconeogenesis is required to maintain glucose levels in the fasting state and inhibition of gluconeogenesis may result in hypoglycemia.

Discuss (5) | Improve

Next question

Hypoglycaemia

Causes
- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
  - causes exaggerated insulin secretion
  - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia

- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
  - Sweating
  - Shaking
  - Hunger
  - Anxiety
  - Nausea
- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
  - Weakness
  - Vision changes
  - Confusion
  - Dizziness
- Severe and uncommon features of hypoglycaemia include:
  - Convulsion
  - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):
  - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
  - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
  - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
  - If the patient is alert, a quick-acting carbohydrate may be given (as above)
  - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
  - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

PassMedicine

← Question 31 of 414 ✗ ⚐ →

Which of the following results establishes a diagnosis of diabetes mellitus?

	Asymptomatic patient with fasting glucose 7.9 mmol/L on one occasion	11%
	Symptomatic patient with fasting glucose 6.8 mmol/L on two occasions	26%
	Glycosuria +++	3%
🟥	Asymptomatic patient with random glucose 22.0 mmol/L on one occasion	9%
🟩	Symptomatic patient with random glucose 12.0 mmol/L on one occasion	52%

Diabetes meliitus diagnosis: fasting > 7.0, random > 11.1 - if asymptomatic need two readings

Important for me Less important

👍 👎 Discuss (5) Improve

Next question

Diabetes mellitus (type 2): diagnosis ★

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic: CKS

- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

When HbA1c is used for the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis: CKS

- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

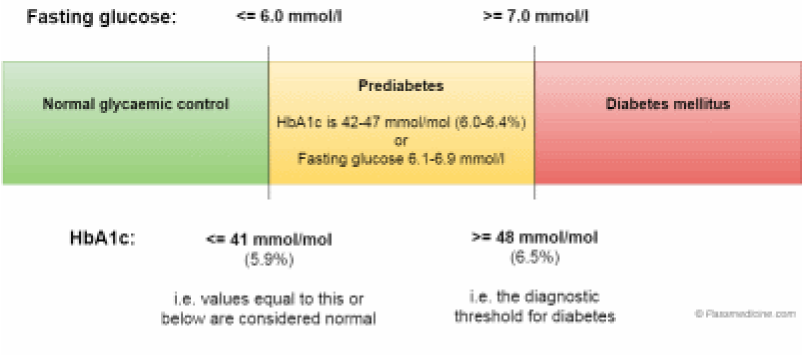

Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
© Passmedicine.com

Diagram showing the spectrum of diabetes diagnosis

Impaired fasting glucose and impaired glucose tolerance

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:

- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 2 👎 1

Type 2 diabetes mellitus: diagnosis

NICE 👍 2 👎 2

2022 Type 2 diabetes guidelines

Diabetes UK 👍 3 👎 4

New diagnostic criteria for diabetes

Report broken link

Media

PassMedicine

Question 32 of 414 ✗

You are conducting the annual review of a 44-year-old woman who has type 1 diabetes mellitus. You want to assess for diabetic neuropathy affecting the feet.

What is the most appropriate screening test to use?

	A standardised questionnaire	4%
	Doppler flow studies of the dorsalis pedis pulse	3%
	Nerve conduction studies	10%
🟥	Test sensation using cotton wool	12%
🟩	Test sensation using a 10 g monofilament	71%

A 10 g monofilament should be used to assess for diabetic neuropathy in the feet

Important for me Less important

The correct answer is **Test sensation using a 10 g monofilament**. This test is recommended by the National Institute for Health and Care Excellence (NICE) in the UK as it is simple, quick, and effective at identifying loss of protective foot sensation in patients with diabetes. The 10 g monofilament exerts a specific amount of pressure on the skin and patients who cannot feel this pressure are considered to have lost protective foot sensation, which puts them at risk of developing diabetic foot ulcers.

A standardised questionnaire can be useful in assessing symptoms associated with neuropathy such as pain or tingling. However, it does not adequately assess loss of protective sensation which is crucial for preventing foot ulcers.

Doppler flow studies of the dorsalis pedis pulse would be more appropriate for assessing peripheral arterial disease rather than neuropathy. While people with diabetes are at increased risk of both conditions, these tests do not evaluate sensory function.

Nerve conduction studies are used to diagnose and evaluate the severity of peripheral neuropathy but they are not practical for routine screening due to their complexity and cost. They also require specialist interpretation.

Testing sensation using **cotton wool** can provide some information about light touch sense but it's less sensitive than the 10 g monofilament test for detecting loss of protective foot sensation. Therefore, while it may be useful as part of a comprehensive neurological examination, it is not sufficient on its own as a screening tool for diabetic neuropathy affecting the feet.

👍 👎 Discuss (1) Improve

Next question

Diabetic foot disease

Diabetic foot disease is an important complication of diabetes mellitus which should be screen for on a regular basis. NICE produced guidelines relating to diabetic foot disease in 2015.

It occurs secondary to two main factors:
- neuropathy: resulting in loss of protective sensation (e.g. not noticing a stone in the shoe), Charcot's arthropathy, dry skin
- peripheral arterial disease: diabetes is a risk factor for both macro and microvascular ischaemia

Presentations
- neuropathy: loss of sensation
- ischaemia: absent foot pulses, reduced ankle-brachial pressure index (ABPI), intermittent claudication
- complications: calluses, ulceration, Charcot's arthropathy, cellulitis, osteomyelitis, gangrene

All patients with diabetes should be screened for diabetic foot disease on at least an annual basis
- screening for ischaemia: done by palpating for both the dorsalis pedis pulse and posterial tibial artery pulse
- screening for neuropathy: a 10 g monofilament is used on various parts of the sole of the foot

NICE recommend that we risk stratify patients:

Low risk	Moderate risk	High risk
• no risk factors except callus alone	• deformity or • neuropathy or	• previous ulceration or • previous amputation or

Low risk	**Moderate risk**	**High risk**
	• non-critical limb ischaemia.	• on renal replacement therapy or • neuropathy and non-critical limb ischaemia together or • neuropathy in combination with callus and/or deformity or • non-critical limb ischaemia in combination with callus and/or deformity.

All patients who are moderate or high risk (I.e. any problems other than simple calluses) should be followed up regularly by the local diabetic foot centre.

Next question

Textbooks

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Extended textbook

Links

NICE 3 3

Diabetic foot problems: prevention and management

Report broken link

Score: **31.3%**

PassMedicine

← Question 33 of 414 ✓ →

A 61-year-old woman is admitted to the Acute Medical Unit as she is generally unwell with muscle twitching. Blood pressure is recorded at 114/78 mmHg, pulse 84/min and she is apyrexial. Blood tests reveal the following:

Calcium	1.94 mmol/l
Albumin	38 g/l

Which one of the following tests is most useful in elucidating the cause of her symptoms?

Urea	1%
Vitamin D	15%
Phosphate	7%
Parathyroid hormone	70%
Magnesium	7%

Parathyroid hormone is the single most useful test in determining the cause of hypocalcaemia

Discuss (8) Improve

Next question

Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- vitamin D deficiency (osteomalacia)
- chronic kidney disease
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)

- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion
- acute pancreatitis

Contamination of blood samples with EDTA may also give falsely low calcium levels.

Management

- severe hypocalcaemia (e.g. carpopedal spasm, tetany, seizures or prolonged QT interval) requires IV calcium replacement
  - the preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
  - intravenous calcium chloride is more likely to cause local irritation
  - ECG monitoring is recommended
- further management depends on the underlying cause

Next question

Textbooks

High-yield textbook

Extended textbook

Media

HYPOCALCEMIA

Hypocalcemia

Osmosis - YouTube

PassMedicine

Question 34 of 414 ✓

Which one of the following types of thyroid cancer is associated with the RET oncogene?

Anaplastic	8%
Lymphoma	3%
Follicular	9%
Medullary	74%
All types of thyroid cancer	6%

The RET oncogene encodes a receptor tyrosine kinase and is associated with MEN type 2.

Papillary thyroid cancer also appears to be associated with the RET oncogene

Discuss (1) Improve

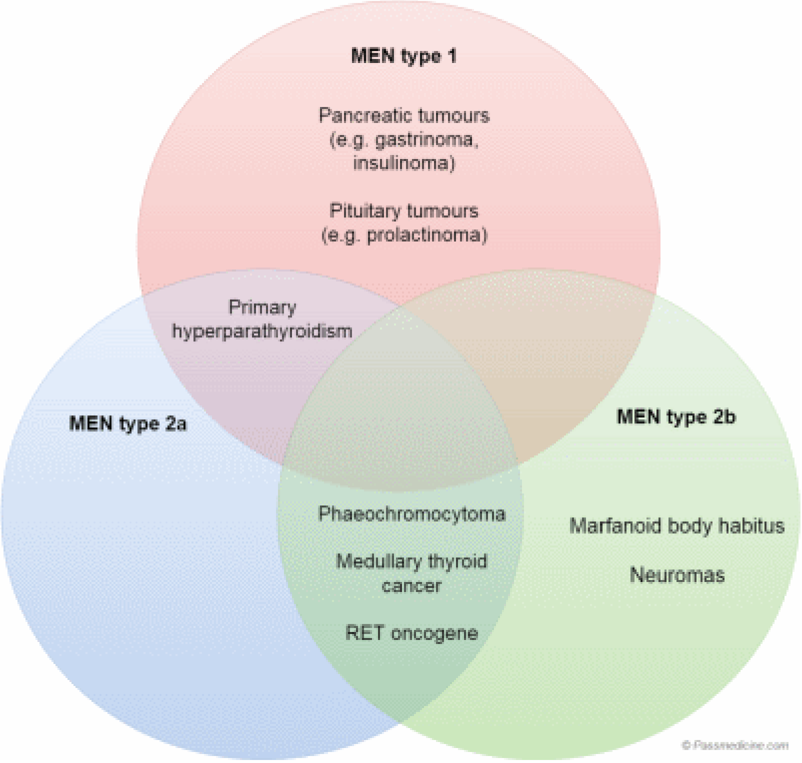
Next question

Multiple endocrine neoplasia ★

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma,	Medullary thyroid cancer (70%) 2 **P**'s	Medullary thyroid cancer 1 **P**

MEN type I	**MEN type IIa**	**MEN type IIb**
gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	**P**arathyroid (60%) **P**haeochromocytoma	**P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
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Venn diagram showing the different types of MEN and their associated features

Next question

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Question 35 of 414 ✕

A 26-year-old woman presents to her GP with a facial rash which she feels is affecting her confidence and self-esteem. This has appeared, and been gradually getting worse, over the past couple of weeks. She has no other symptoms and feels well. On examination, she has a monomorphic papular rash across most of the face; there are no comedones or cysts visible.

Her only past medical history is a number of allergies, for which she was referred to an allergy consultant. Two months ago she was commenced on 15mg prednisolone daily. She takes no other medications and has no significant family history.

What is the definitive management for the likely condition?

	Oral antibiotic and topical retinoid	9%
🟥	Oral retinoid	4%
	Stop prednisolone	14%
🟩	Taper prednisolone gradually	66%
	Topical antibiotic and topical retinoid	8%

Systemic glucocorticoids can cause drug-induced acne. This is characterised as monomorphic papular rash without comedones or cysts. This does not respond to acne treatment but improves on drug discontinuation

Important for me Less important

The correct answer is tapering prednisolone gradually. The history here points towards a diagnosis of drug-induced acne, which can be caused by systemic glucocorticoids. Drug-induced acne generally presents with this rash without comedones or cysts, whereas normal acne vulgaris has both comedones and cysts. Drug-induced acne will not respond to normal acne treatment, but will improve once the offending drug is discontinued. Given the dose and length of time that the patient has been taking it there is a risk of adrenal suppression so prednisolone should be gradually withdrawn.

Stopping prednisolone suddenly is incorrect - given the length of the course so far, it should be tapered off.

Topical antibiotic and topical retinoid is incorrect - this would be the step-up in management, from a topical retinoid alone, for acne vulgaris.

An oral antibiotic with a topical retinoid would be incorrect - this is the next step-up for acne vulgaris management. The topical retinoid should always be co-prescribed with the oral antibiotic to reduce the risk of resistance development.

An oral retinoid is incorrect - this would be management for severe acne vulgaris, and only initiated by a dermatologist, rather than in primary care.

👍 👎 Discuss (3) Improve

Next question

Corticosteroids: side-effects ★

Glucocorticoid side-effects

- endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, hyperlipidaemia
- Cushing's syndrome: moon face, buffalo hump, striae
- musculoskeletal: osteoporosis, proximal myopathy, avascular necrosis of the femoral head
- immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis
- psychiatric: insomnia, mania, depression, psychosis
- gastrointestinal: peptic ulceration, acute pancreatitis
- ophthalmic: glaucoma, cataracts
- dermatological: acne
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Next question

PassMedicine

Question 36 of 414 ✓

A 60-year-old woman with a background of pheochromocytoma presents with a lump in her neck. She is diagnosed with medullary thyroid cancer.

What gene is associated with this malignancy?

APC	1%
BRCA1	1%
EGFR	1%
MEN1 gene	21%
RET oncogene	76%

Medullary thyroid cancer is associated with the RET oncogene

Important for me Less important

This patient has multiple endocrine neoplasia (MEN) type 2a or 2b, which are both associated with medullary thyroid cancer and the **RET oncogene**. The RET gene encodes a transmembrane receptor tyrosine kinase. Germline mutations in RET are found in most MEN2 patients.

Mutations in **EGFR** are associated with non-small cell lung cancer.

BRCA1 is a tumour suppressor gene which when mutated can cause breast and ovarian cancer.

The **MEN1** gene is associated with MEN type 1. MEN type 1 is not associated with medullary thyroid cancer, therefore this option is incorrect.

Mutations in **APC** gene cause familial adenomatous polyposis which is associated with colorectal cancer.

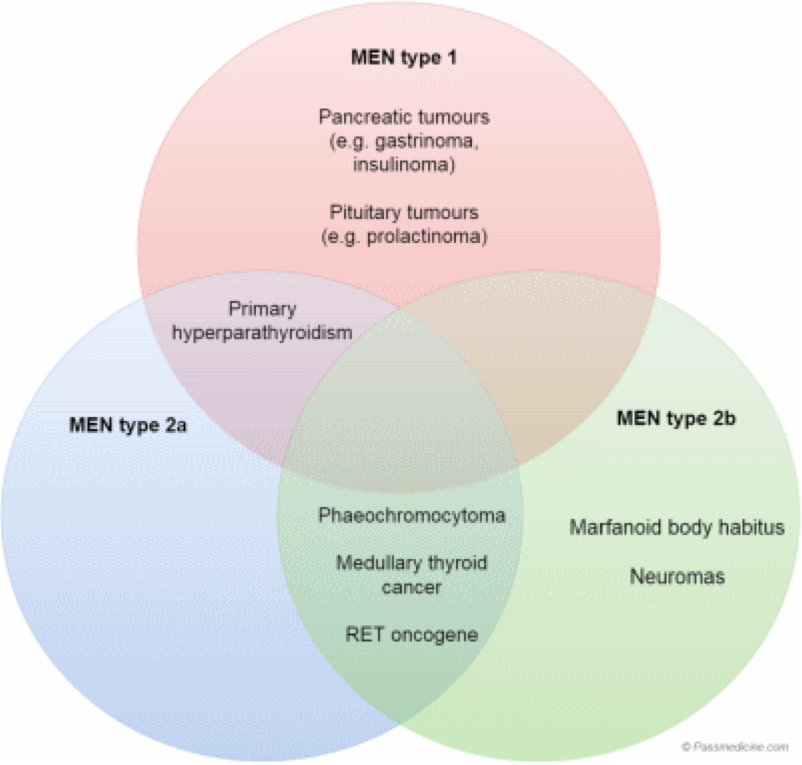
Discuss Improve

Next question

Multiple endocrine neoplasia ★

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	Medullary thyroid cancer 1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
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Venn diagram showing the different types of MEN and their associated features

Next question

Textbooks

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Media

PANCREATIC
NEUROENDOCRINE
NEOPLASMS

Pancreatic neuroendocrine neoplasms

Osmosis - YouTube 👍 17 👎 3

Report broken media

Score: **36.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗

PassMedicine

Question 37 of 414 ✓

A 65-year-old woman has uncontrolled diabetes despite lifestyle changes and treatment with metformin. Her body mass index is 32 kg/m^2. Her GP commences treatment with sitagliptin.

What is the main mechanism of action of this drug?

Increases pancreatic insulin secretion	9%
Increases peripheral insulin sensitivity	8%
Reduces hepatic gluconeogenesis	4%
Reduces the peripheral breakdown of incretins	75%
Reduces the release of glucagon	4%

Gliptins (DPP-4 inhibitors) reduce the peripheral breakdown of incretins such as GLP-1

Important for me Less important

The correct answer is that sitagliptin reduces the peripheral break down of incretins. Sitagliptin is one of the Gliptins (DPP-4 inhibitors) which reduce the peripheral breakdown of incretins such as GLP-1.

Metformin increases peripheral insulin sensitivity and reduces hepatic gluconeogenesis.

Sulfonylureas augment pancreatic insulin secretion. Increased insulin secretion can lead to hypoglycaemia.

GLP mimetics, e.g. exenatide, augment pancreatic insulin secretion, suppress glucagon release, slow gastric emptying and promote satiety.

Discuss (4) Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points
- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

High-yield textbook

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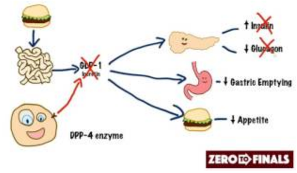
Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

Report broken link

Media


↑ Insulin
↓ Glucagon
GLP-1
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

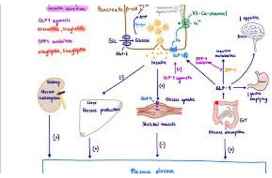
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2

The role of "GLP" system in tt of diabetes
Sitagliptin
(−)
inactive GLP-1
DPP-4
incretin
"GLP"
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 26 👎 5

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Question 38 of 414 ✗

A 25-year-old man with a family history of multiple endocrine neoplasia type 1 is reviewed in clinic. What is the single most useful investigation to monitor such patients?

Short synacthen test	6%
🟥 Urinary catecholamines	14%
🟩 Serum calcium	61%
Thyroid function tests	8%
Serum prolactin	12%

Peptic ulceration, galactorrhoea, hypercalcaemia - multiple endocrine neoplasia type I

Important for me Less important

The high incidence of parathyroid tumours and hypercalcaemia make serum calcium a useful indicator of MEN type 1 in suspected individuals

Discuss (1) Improve

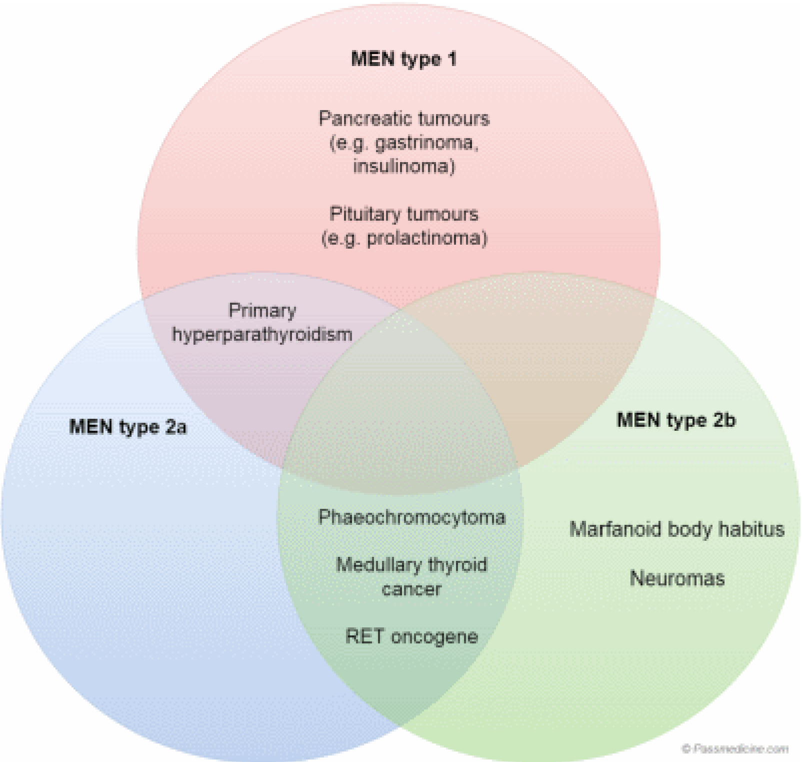
Next question

Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	MEN type IIa	MEN type IIb
3 **P**'s	Medullary thyroid cancer (70%)	Medullary thyroid cancer

MEN type I	MEN type IIa	MEN type IIb
Parathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
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Venn diagram showing the different types of MEN and their associated features

Next question

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Question 39 of 414 ✗

A 60-year-old man who is known to have lung cancer comes for review. For the past three weeks he has lost his appetite, has been feeling sick and generally feels tired. On examination he appears to be mildly dehydrated. You order some blood tests:

Calcium	3.12 mmol/l
Albumin	40 g/l
Glucose (random)	6.7 mmol/l
Urea	10.2 mmol/l
Creatinine	115 µmol/l

Which one of his existing medications is most likely to be contributing to his presentation?

	Amlodipine	4%
🟥	Simvastatin	3%
🟩	Bendroflumethiazide	86%
	Aspirin	1%
	Lisinopril	6%

Thiazides cause hypercalcaemia

Important for me Less important

The correct answer is **Bendroflumethiazide**. This patient is presenting with symptoms of hypercalcaemia (loss of appetite, nausea, fatigue) and the blood test results confirm an elevated calcium level of 3.12 mmol/l. Bendroflumethiazide is a thiazide diuretic which can cause hypercalcaemia by increasing renal tubular reabsorption of calcium. In this case, the patient's existing lung cancer could also contribute to his hypercalcaemia due to paraneoplastic production of parathyroid hormone-related protein (PTHrP). However, it is important to consider medication side effects in the clinical context.

Amlodipine is a calcium channel blocker used for treating hypertension and angina. It does not typically cause hypercalcaemia or any of the symptoms described in this case.

Simvastatin is a statin used for lowering cholesterol levels and reducing cardiovascular risk. It can cause myalgia and hepatic dysfunction but does not usually lead to hypercalcaemia or contribute to this patient's presentation.

Aspirin is an antiplatelet agent and analgesic commonly used for pain relief and prevention of cardiovascular events. While it may cause gastrointestinal side effects such as dyspepsia or gastric ulcers, it does not have a direct effect on calcium levels.

Finally, **Lisinopril** is an angiotensin-converting enzyme (ACE) inhibitor used for managing hypertension and heart failure. It may cause side effects like cough, hypotension, or renal dysfunction but does not typically result in hypercalcaemia.

👍 👎 Discuss (4) Improve

Next question

Hypercalcaemia: causes

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
  - PTHrP from the tumour e.g. squamous cell lung cancer
  - bone metastases
  - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include

- sarcoidosis
  - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:

  - thiazides
  - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
  - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

Textbooks

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Extended textbook

Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€“ presentation and management

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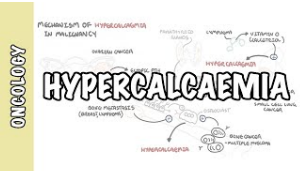
Media



Hypercalcemia in malignancy

Armando Hasudungan - YouTube 👍 19 👎 2

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Question 40 of 414 ✕ ⚐

A 21-year-old medical student is referred to the clinic with polyuria and polydipsia. She is concerned she may have developed diabetes after a recent lecture on the topic.

Her only past medical history is anxiety and depression. She takes no regular medications.

Her GP has performed some blood tests.

Na^+	138 mmol/L	(135 - 145)
K^+	3.9 mmol/L	(3.5 - 5.0)
Urea	3.2 mmol/L	(2.0 - 7.0)
Creatinine	66 µmol/L	(55 - 120)
Bilirubin	10 µmol/L	(3 - 17)
ALP	132 u/L	(30 - 100)
ALT	25 u/L	(3 - 40)
Albumin	36 g/L	(35 - 50)
Calcium	2.99 mmol/L	(2.1-2.6)
Phosphate	0.67 mmol/L	(0.8-1.4)
Parathyroid hormone (PTH)	6.2 pmol/L	(1.6 - 6.9)
Fasting glucose	4.3 mmol/L	(3.9 - 5.4)

What is the most likely cause of her symptoms?

	Diabetes mellitus	1%
🟥	Hypoparathyroidism	2%
🟩	Primary hyperparathyroidism	75%
	Secondary hyperparathyroidism	15%
	Tertiary hyperparathyroidism	7%

The PTH level in primary hyperparathyroidism may be normal

Important for me Less important

It is important to remember that with hypercalcaemia the normal response would be a low PTH. A high or normal PTH in the context of hypercalcaemia usually indicates **primary hyperparathyroidism** which is the correct answer in this case.

Secondary hyperparathyroidism is incorrect. This is a physiological elevation of PTH levels in response to hypocalcaemia. It is commonly due to renal failure or vitamin D deficiency. The hypercalcaemia here makes this the wrong answer.

Tertiary hyperparathyroidism is also incorrect. It is often seen in patients with end-stage renal failure and is thought to be due to prolonged secondary hyperparathyroidism which results in the inappropriate continued release of PTH despite normalisation of calcium levels.

Diabetes mellitus is not the correct answer, despite the patient's concern. It has been excluded with a normal fasting blood glucose as she would need to have significant hyperglycaemia to cause the osmotic symptoms of polyuria and polydipsia.

There is no evidence of **hypoparathyroidism** as you would expect to see a low calcium and low PTH with a high phosphate. This is therefore incorrect. There may also be symptoms of hypocalcaemia such as twitching, paraesthesia and tetany.

👍 👎 Discuss (1) Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':

- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations

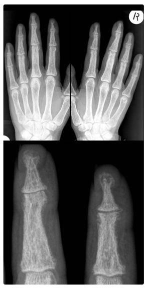
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- bloods
  - raised calcium, low phosphate
  - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
  - pepperpot skull
  - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
  - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



Next question

Textbooks

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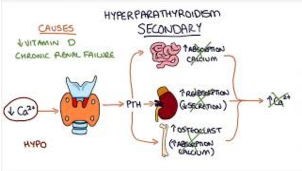
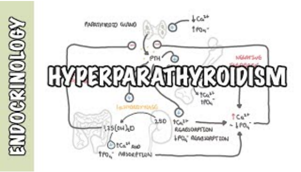
Media


HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
PTH
HYPO

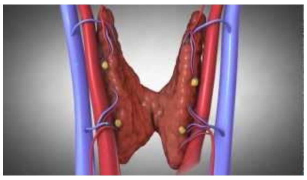
Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2



Parathyroid Glands and Hyperparathyroidism

Norman Parathyroid Center - YouTube 👍 20 👎 5

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Question 41 of 414 ✗

A 56-year-old female is admitted to ITU with a severe pneumonia. Thyroid function tests are most likely to show:

	TSH normal; thyroxine high; T3 high	13%
🟩	TSH normal / low; thyroxine low; T3 low	56%
	TSH high; thyroxine low; T3 low	10%
🟥	TSH low; thyroxine high; T3 high	11%
	TSH high; thyroxine normal; T3 high	10%

The correct answer is **TSH normal / low; thyroxine low; T3 low**. This pattern of thyroid function tests is indicative of a non-thyroidal illness syndrome (NTIS), also known as euthyroid sick syndrome, which is commonly seen in critically ill patients. In this condition, there is a decrease in serum triiodothyronine (T3) and thyroxine (T4) levels, with a normal or slightly decreased thyroid-stimulating hormone (TSH). The exact mechanism behind NTIS remains unclear, but it's believed to be an adaptive response to severe illness.

TSH normal; thyroxine high; T3 high would suggest hyperthyroidism. However, severe pneumonia does not typically cause hyperthyroidism.

TSH high; thyroxine low; T3 low indicates primary hypothyroidism. While hypothyroidism can predispose to infections due to impaired immune responses, it would not be caused by an acute infection such as pneumonia.

TSH low; thyroxine high; T3 high represents secondary or tertiary hyperthyroidism resulting from pituitary or hypothalamic disease respectively. Again, this wouldn't be caused by pneumonia.

Finally, **TSH high; thyroxine normal; T3 high** could indicate resistance to thyroid hormone (RTH), a rare inherited disorder characterised by elevated levels of TSH despite normal or increased levels of thyroid hormones. RTH has no association with pneumonia and thus would not fit the patient's clinical picture.

Discuss (4) | Improve

Next question

Sick euthyroid syndrome ★

In sick euthyroid syndrome (now referred to as non-thyroidal illness) it is often said that everything (TSH, thyroxine and T3) is low. In the majority of cases however the TSH level is within the >normal range (inappropriately normal given the low thyroxine and T3).

Changes are reversible upon recovery from the systemic illness and hence no treatment is usually needed.

Next question

Textbooks

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Score: **34.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗

PassMedicine

Question 42 of 414 ✗

A 71-year-old woman with a history of type 2 diabetes mellitus presents with lethargy and polyuria. A diagnosis of hyperosmolar hyperglycaemic state is considered. Which one of the following findings would be least consistent with this diagnosis?

	pH of 7.38	10%
	Ketones 1+ in urine	29%
🟩	Serum osmolality of 310 mosmol/kg	30%
🟥	Serum bicarbonate of 19 mmol/l	21%
	Glucose of 45 mmol/l	10%

A trace of ketones may be found in hyperosmolar hyperglycaemic state. Serum osmolality is typically > 320 mosmol/kg

Discuss (10) Improve

Next question

Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) is a medical emergency that can be difficult to manage and has a significant associated mortality (up to 20%). Hyperglycaemia results in osmotic diuresis, severe dehydration, and electrolyte deficiencies. HHS typically presents in the elderly with type 2 diabetes mellitus (T2DM).

Pathophysiology

- hyperglycaemia → ↑ serum osmolality → osmotic diuresis → severe volume depletion

Precipitating factors

- intercurrent illness
- dementia

- sedative drugs

Clinical features

- whilst DKA presents within hours of onset, HHS comes on over many days, and consequently, the dehydration and metabolic disturbances may be more extreme
- consequences of volume loss
  - clinical signs of dehydration
  - polyuria
  - polydipsia
- systemic
  - lethargy
  - nausea and vomiting
- neurological
  - altered level of consciousness
  - focal neurological deficits
- haematological
  - hyperviscosity (may result in myocardial infarctions, stroke and peripheral arterial thrombosis)

There are no precise **diagnostic criteria** but the following are typically seen

- hypovolaemia
- marked hyperglycaemia (>30 mmol/L)
- significantly raised serum osmolarity (> 320 mosmol/kg)
  - can be calculated by: $2 * Na^+$ + glucose + urea
- no significant hyperketonaemia (<3 mmol/L)
- no significant acidosis (bicarbonate > 15 mmol/l or pH > 7.3 - acidosis can occur due to lactic acidosis or renal impairment)

Management

- fluid replacement
  - fluid losses in HHS are estimated to be between 100 - 220 ml/kg
  - IV 0.9% sodium chloride solution
  - typically given at 0.5 - 1 L/hour depending on clinical assessment
  - potassium levels should be monitored and added to fluids depending on the level
- insulin
  - should not be given unless blood glucose stops falling while giving IV fluids
- venous thromboembolism prophylaxis
  - patients are at risk of thrombosis due to hyperviscosity

Complications

- vascular complications may occur due to hyperviscosity:
    - such as myocardial infarction
    - stroke

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Joint British Diabetes Societies 👍 1 👎 0

The management of the hyperosmolar hyperglycaemic state (HHS)

Report broken link

Score: **33.3%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗

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Question 43 of 414 ✗

A 5-year-old boy presents to the emergency department with polyuria and polydipsia. He appears fatigued and has experienced vomiting twice in the past 24 hours. On examination, he is found to have reduced skin turgor and dry mucous membranes, with a blood pressure of 121/67 mmHg.

The results of his blood tests are as follows:

Na$^+$	138 mmol/L	(135 - 145)
K$^+$	2.7 mmol/L	(3.5 - 5.0)
Mg$^+$	0.85 mmol/L	(0.8-1)
Bicarbonate	34 mmol/L	(22 - 29)
Urea	12.3 mmol/L	(2.0 - 7.0)
Creatinine	65 µmol/L	(55 - 120)

pH	7.51	(7.35-7.45)

A rare inherited renal condition is suspected.

What is the cause of the most likely diagnosis?

🟩	A defective NKCC2 channel in the ascending loop of Henle	68%
	A defective epithelial sodium channel	5%
🟥	A defective thiazide-sensitive sodium-chloride co-transporter	12%
	Failure of acid excretion in the distal convoluted tubule	6%
	Primary hyperaldosteronism caused by an adrenal adenoma	8%

Bartter's syndrome results from a defective NKCC2 channel in the ascending loop of Henle

Important for me Less important

Bartter's syndrome is attributable to **a defective NKCC2 channel in the ascending loop of Henle**. It is a genetic condition that arises from a defect in chloride reabsorption at the Na+ K+

2Cl- cotransporter (NKCC2) within the ascending limb of the loop of Henle. This abnormality leads to marked hypokalaemia, as demonstrated in this patient. The compromised chloride reabsorption interferes with the proper exchange of bicarbonate for chloride, leading to increased levels of bicarbonate in the blood and consequent metabolic alkalosis. Additionally, Bartter's syndrome results in elevated renin and aldosterone levels, which promote hydrogen ion excretion and further aggravate the alkalosis. A characteristic feature of Bartter's syndrome is normotension, which concurs with our case presentation.

Liddle's syndrome stems from **a defective epithelial sodium channel**. This disorder presents with hypokalaemic metabolic alkalosis along with hypertension. Considering that our patient has normal blood pressure readings, Liddle's syndrome can be confidently excluded.

Gitelman's syndrome involves a defect in the **thiazide-sensitive sodium-chloride cotransporter** and shares many features with Bartter's syndrome. Clinical manifestations include dehydration, hypokalaemia, hypomagnesaemia, hypocalciuria, metabolic alkalosis and normotension. Typically manifesting during adolescence or early adulthood, Gitelman's syndrome could be considered. Nonetheless, since our patient has normal magnesium levels, Bartter's syndrome remains more likely.

Failure of acid excretion in the distal convoluted tubule underpins type 1 renal tubular acidosis. While this condition also presents with hypokalaemia, it is typically associated with metabolic acidosis rather than alkalosis as observed in our patient.

Conn's syndrome constitutes a form of **primary hyperaldosteronism due to an adrenal adenoma**, leading to hypokalaemia and hypertension - features not seen in our normotensive patient. Conn's syndrome is less frequently encountered as a cause of primary hyperaldosteronism than bilateral adrenal hyperplasia. Differentiation between these two entities can be facilitated by adrenal venous sampling.

👍 👎 Discuss (1) Improve

Next question

Bartter's syndrome ★

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na$^+$ K$^+$ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 9 👎 3

2012 Renal tubular disorders review

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Score: **32.6%**

1 ✓

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Question 44 of 414 ✗

Liddle's syndrome is associated with each one of the following, except:

Alkalosis	13%
Response to treatment with amiloride	20%
Hypertension	15%
🟩 Autosomal recessive inheritance	39%
🟥 Hypokalaemia	11%

Discuss (6) Improve

Next question

Liddle's syndrome ★

Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

Treatment is with either amiloride or triamterene

Next question

PassMedicine

Question 45 of 414 ✗

A man presents to his GP with a tender mass in his neck. He reports it has only recently become apparent, but it seems to be growing rapidly. On questioning, he reports he has noticed some weight loss and sometimes wakes at night very sweaty and has to change his pillow-case. He denies any recent illnesses and reports no symptoms of palpitations, anxiety, or trembling.

Thyroid function tests are normal and an ultrasound scan of the neck is performed, which shows an enlarged thyroid gland. He goes on to have a fine-needle aspiration biopsy and finally a surgical biopsy of the gland which reveals a thyroid lymphoma.

Which of these is an associated risk factor for this condition?

	Being male	2%
🟥	Exposure to radiation	11%
🟩	Past medical history of Hashimoto's thyroiditis	79%
	Smoking	8%
	Young age	1%

Hashimoto's thyroiditis is associated with thyroid lymphoma

Important for me Less important

This man has been diagnosed with thyroid lymphoma, this is a rare disease that is linked with Hashimoto's thyroiditis, therefore that is the correct answer.

Being male is incorrect as thyroid lymphoma is more common in women.

Radiation is incorrect as this is a risk factor for other forms of thyroid cancer, but not for thyroid lymphoma.

Smoking and thyroid cancer remains a heavily researched topic. However, there is currently no correlation between smoking and increased risk of thyroid cancer. In fact, some studies show an inverse relationship between smoking and thyroid cancer, while other studies found no association.

Young age is incorrect as thyroid lymphoma most commonly occurs between the ages of 65 to 75 years.

👍 👎 Discuss Improve

Next question

Thyroid cancer ★

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's thyroiditis

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	• Usually contain a mixture of papillary and colloidal filled follicles • Histologically tumour has papillary projections and pale empty nuclei • Seldom encapsulated

Type	Notes
	• Lymph node metastasis predominate • Haematogenous metastasis rare
Follicular adenoma	• Usually present as a solitary thyroid nodule • Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. • Vascular invasion predominates • Multifocal disease raree
Medullary carcinoma	• C cells derived from neural crest and not thyroid tissue • Serum calcitonin levels often raised • Familial genetic disease accounts for up to 20% cases • Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.
Anaplastic carcinoma	• Most common in elderly females • Local invasion is a common feature • Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

Next question

Textbooks

High-yield textbook

Extended textbook

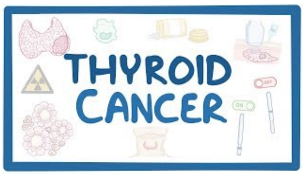
Links

British Thyroid Association 👍 3 👎 3

2014 Guidelines for the Management of Thyroid Cancer

Report broken link

Media



Thyroid cancer

Osmosis - YouTube 👍 20 👎 1

Thyroid Nodule

Armando Hasudungan - YouTube 👍 12 👎 4

Report broken media

Score: **31.1%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓

PassMedicine

Question 46 of 414 ✗

A 45-year-old woman presents with weight gain and recurrent 'dizzy' episodes. Over the past four months she has gained 20 kg. The episodes occur on an almost daily basis and are characterised by blurred vision, sweating, headaches and palpitations. Her GP checked a blood sugar during one of these episodes which was record as being 1.4 mmol/l. What is the single most useful test?

	Glucagon stimulation test	6%
🟥	Oral glucose tolerance test with growth hormone measurements	12%
🟩	Insulin + C-peptide levels during a hypoglycaemic episode	62%
	Short ACTH test	12%
	Insulin tolerance test	8%

This patient has symptoms typical of an insulinoma. Whilst supervised fasting is normally the investigation of choice if this option is not given then insulin + C-peptide levels during an acute hypoglycaemic episode are useful.

Discuss (7) | Improve

Next question

Insulinoma

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics

- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

Features

- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis

- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Management

- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

Next question

Textbooks

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Media

PANCREATIC NEUROENDOCRINE NEOPLASMS

Pancreatic neuroendocrine neoplasms

Osmosis - YouTube 👍 19 👎 0

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Question 47 of 414 ✗

A 32-year-old woman who is 24 weeks pregnant with her third child comes to the clinic for review. She has been diagnosed with gestational diabetes mellitus, and a fasting plasma glucose following 2 weeks of adherence to lifestyle changes is still elevated at 6.8 mmol/l. Her blood pressure is 122/82 mmHg, and her body mass index is 25 kg/m^2. She is reluctant to start insulin initially because her sister has Type 1 diabetes and suffers from frequent hypoglycaemia.

Which of the following is the most appropriate next intervention?

Metformin	76%
Glibenclamide	7%
Insulin glargine	10%
Dapagliflozin	2%
Insulin pump therapy	5%

Metformin is the first line therapy of choice for diabetes in pregnancy

Important for me Less important

Metformin has been evaluated in a large Australasian trial for the treatment of gestational diabetes mellitus. Versus insulin initiation at the point of diagnosis, those patients treated with metformin gained less weight during pregnancy and suffered slightly fewer episodes of hypoglycaemia. There was no difference in the primary endpoint of adverse foetal outcomes, and women treated with metformin first preferred this option, even though most eventually progressed to insulin in addition to oral therapy. This has precipitated NICE to recommend metformin as a first line option where fasting glucose is less than 7.0 mmol/l despite dietary modification.

https://www.nejm.org/doi/full/10.1056/NEJMoa0707193
https://www.nice.org.uk/guidance/ng3

Although glibenclamide is safe in pregnancy it does not limit weight gain and control is inferior to insulin therapy. It's therefore only an option in patients who refuse metformin and insulin. Out of the insulin options listed, insulin pump therapy is preferred, although many women find it more difficult to comply with pump therapy and are therefore treated with a basal bolus regimen. There is no evidence to support the use of SGLT-2 inhibitors such as dapagliflozin in pregnancy. One problem which leads to diabetes is relative insulin resistance, which SGLT-2 inhibitors will not significantly impact upon.

👍 👎 Discuss (2) Improve

Next question

Gestational diabetes ★

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:

- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes

- BMI of > 30 kg/m^2
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	**Target**
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

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Extended textbook

Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

NICE 👍 3 👎 5

2015 Management of diabetes in pregnancy

Report broken link

Media

Gestational Diabetes

Armando Hasudungan - YouTube 👍 15 👎 3

Report broken media

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Question 48 of 414 ✓

A 38-year-old male is admitted to the Emergency Department following a collapse while running a marathon. His blood results are as follows:

Na+	121 mmol/l
K+	3.4 mmol/l
Urea	3.2 mmol/l
Creatinine	68 umol/l

During assessment he becomes increasingly obtunded and goes on to have multiple tonic clonic seizures. What is the most appropriate treatment from the list below to improve his neurological status?

Decompressive craniotomy	1%
Demeclocycline	2%
Intravenous normal saline	17%
Hypertonic saline	76%
Mannitol	5%

Acute hyponatraemia is that which occurs within a duration of 48 hours.

Over consumption of fluids, prolonged race duration and inadequate training all can predispose to acute hyponatraemia in this setting. When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result patients may die from brain herniation.

The correct treatment to give is hypertonic saline. Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment. Demeclocycline is used for SIADH and mannitol is more likely to be used in the context of traumatic brain injury.

A small, quick increase in the serum sodium is required in order to decrease intracranial pressure. Hypertonic saline (3%) boluses (after seeking senior advice) are the most appropriate treatment to improve neurological status in such patients.

👍 👎 Discuss (6) Improve

Next question

Hyponatraemia: treatment

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:
- duration of hyponatremia: is it acute or chronic?
    - acute: develops over a period of < 48 hours
    - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
    - mild: 130-134 mmol/L
    - moderate: 120-129 mmol/L
    - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
    - patients with mild hyponatraemia may be symptomatic
    - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
    - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
    - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
    - euvolemic hyponatraemia: SIADH
    - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected

- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
    - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
    - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider medications:
    - demeclocycline
    - vaptans (see below)

If a hypervolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):

- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia

- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia
- pathophysiology:
  - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
  - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

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Question 49 of 414 ×

A 22 year-old man is referred to clinic with refractory hypertension.

Potassium	2.7mmol/l

Other U&E, FBC, calcium and LFTs are normal. Which would be the most appropriate next investigation?

CT abdomen	4%
MR angiography renal tract	2%
24 hour urinary catecholamines	11%
USS abdomen	2%
Plasma renin and aldosterone levels	81%

The differential for hypertension with low potassium includes Conn's, Cushing's, renal artery stenosis and Liddle's. The first step in this case should be further simple investigations. Quantifying the renin and angiotensin levels will help to distinguish the cause here, before going on to more specialised tests.

Cushing's and Conn's would be associated with a high aldosterone and a low renin, renal artery stenosis would be associated with a high renin and aldosterone, Liddle's is associated with a low renin and aldosterone.

Discuss (5) Improve

Next question

Hypokalaemia and hypertension

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not

Hypokalaemia with hypertension

- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
- 11-beta hydroxylase deficiency*

Carbenoxolone, an anti-ulcer drug, and liquorice excess can potentially cause hypokalaemia associated with hypertension

Hypokalaemia without hypertension

- diuretics
- GI loss (e.g. Diarrhoea, vomiting)
- renal tubular acidosis (type 1 and 2**)
- Bartter's syndrome
- Gitelman syndrome

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**type 4 renal tubular acidosis is associated with hyperkalaemia

Next question

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Media

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Question 50 of 414

A 52-year-old woman who was diagnosed as having primary atrophic hypothyroidism 12 months ago is reviewed following recent thyroid function tests (TFTs):

TSH	12.5 mU/l
Free T4	14 pmol/l

She is currently taking 75mcg of levothyroxine once a day. How should these results be interpreted?

🟩	Poor compliance with medication	46%
	Her thyroxine dose needs to be increased	35%
🟥	Evidence of recent systemic steroid therapy	4%
	She is on the correct dose	9%
	T4 to T3 conversion disorder	7%

The TSH level is high. This implies that over recent days/weeks her body is thyroxine deficient. However, her free T4 is within normal range. The most likely explanation is that she started taking the thyroxine properly just before the blood test. This would correct the thyroxine level but the TSH takes longer to normalise.

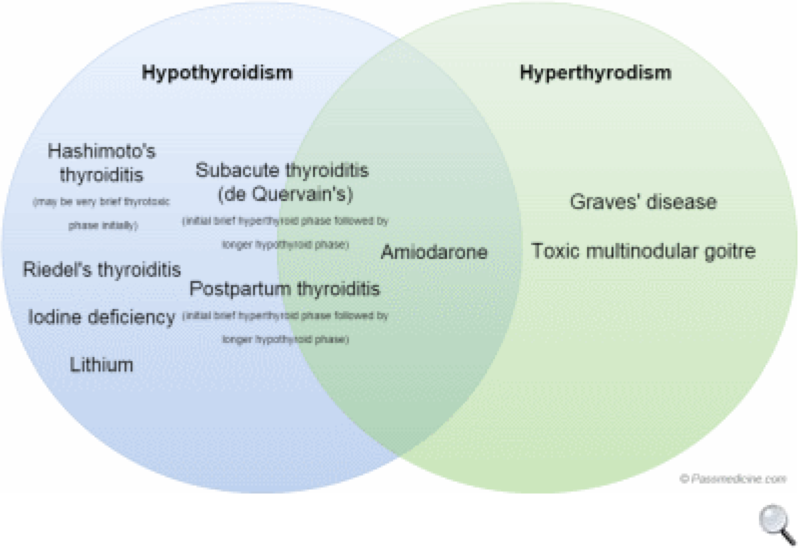
Discuss (4) Improve

Next question

Thyroid function tests

The interpretation of thyroid function tests is usually straightforward:

Diagnosis	TSH	Free T4	Notes
Thyrotoxicosis (e.g. Graves' disease)	Low	High	In T3 thyrotoxicosis the free T4 will be normal
Primary hypothyroidism (primary atrophic hypothyroidism)	High	Low	
Secondary hypothyroidism	Low	Low	Replacement steroid therapy is required prior to thyroxine
Sick euthyroid syndrome*	Low**	Low	Common in hospital inpatients T3 is particularly low in these patients
Subclinical hypothyroidism	High	Normal	
Poor compliance with thyroxine	High	Normal	
Steroid therapy	Low	Normal	


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Graves' disease
Toxic multinodular goitre
Riedel's thyroiditis
Postpartum thyroiditis
Iodine deficiency
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Lithium
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

*now referred to as non-thyroidal illness
**TSH may be normal in some cases

Next question

PassMedicine

Question 51 of 414 ✗

A 51-year-old woman is seen in the Endocrinology clinic for assessment of a thyroid nodule.

Her past medical history is notable for Hashimoto's thyroiditis and rheumatoid arthritis. Her father suffered from type 1 diabetes, and died from a renal tumour in his sixties.

Her medications include levothyroxine and sulfasalazine, as well as over the counter paracetamol.

On examination, she is clinically euthyroid. A small, solitary nodule is palpable on the superior aspect of the right lobe of the thyroid gland. There are no signs of airway compromise.

Her thyroid function tests are as follows:

Thyroid stimulating hormone (TSH)	3.5 mU/L	(0.5-5.5)
Free thyroxine (T4)	11 pmol/L	(9.0 - 18)

.

She proceeds to an ultrasound scan, which confirms a 1cm x 1cm hypoechoic mass in the right lobe of the thyroid.

What is the most likely diagnosis?

	Follicular thyroid carcinoma	13%
🟥	Medullary thyroid carcinoma	11%
	Papillary thyroid carcinoma	10%
	Anaplastic thyroid carcinoma	3%
🟩	Thyroid lymphoma	63%

Hashimoto's thyroiditis is associated with thyroid lymphoma

Important for me Less important

This patient has presented with a thyroid tumour in the context of Hashimoto's thyroiditis. Hashimoto's thyroiditis is characterised by a chronic infiltration of the thyroid gland with B-lymphocytes, which are prone to undergo clonal proliferation. As such, the incidence of thyroid lymphoma is markedly increased amongst patients with Hashimoto's thyroiditis compared to the general population. Thyroid lymphoma is therefore the correct answer.

Both follicular and papillary thyroid carcinomas are plausible diagnoses for a patient of this age, but do not see an increased incidence in the context of Hashimoto's thyroiditis.

Similarly, spontaneous medullary thyroid carcinoma is not associated with Hashimoto's thyroiditis. The family history of a renal tumour is a distractor, and not indicative of underlying multiple endocrine neoplasia type 2 (MEN2), which is associated with adrenal phaeochromocytomas.

Anaplastic thyroid carcinomas tend to be highly aggressive, poorly-differentiated tumours, which are most often seen in patients over the age of 65. They are often associated with airway compromise due to rapid growth.

Discuss (5) Improve

Next question

Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's thyroiditis

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	Usually contain a mixture of papillary and colloidal filled follicles Histologically tumour has papillary projections and pale empty nuclei Seldom encapsulated Lymph node metastasis predominate Haematogenous metastasis rare
Follicular adenoma	Usually present as a solitary thyroid nodule Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. Vascular invasion predominates Multifocal disease raree
Medullary carcinoma	C cells derived from neural crest and not thyroid tissue Serum calcitonin levels often raised Familial genetic disease accounts for up to 20% cases Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.
Anaplastic carcinoma	Most common in elderly females Local invasion is a common feature Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

Next question

Textbooks

High-yield textbook

Extended textbook

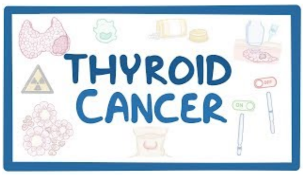
Links

British Thyroid Association 👍 3 👎 3

2014 Guidelines for the Management of Thyroid Cancer

Report broken link

Media



Thyroid cancer

Osmosis - YouTube 👍 20 👎 1

Thyroid Nodule

Armando Hasudungan - YouTube 👍 12 👎 4

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PassMedicine

Question 52 of 414 ✓

A 27-year-old woman presents with excessive thirst and passing large volumes of urine.

Following extensive investigations, a diagnosis of primary polydipsia is suspected.

What results would support this diagnosis?

A known genetic defect in the AVPR2 gene	7%
High urine osmolality after fluid deprivation	77%
Low urine osmolality after desmopressin administration	12%
Medication history including lithium	3%
Past medical history of haemochromatosis	1%

Water deprivation test: primary polydipsia

- urine osmolality after fluid deprivation: high
- urine osmolality after desmopressin: high

Important for me Less important

Primary polydipsia is a condition where there is excessive consumption of fluid leading to the production of large volumes of dilute urine. As there is no physical problem with fluid homeostasis, you would expect the urine to concentrate appropriately after fluid deprivation or following the administration of desmopressin, therefore **high urine osmolality after fluid deprivation** is the correct answer.

Low urine osmolality after desmopressin administration would be expected in nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus is a condition which is caused by ADH insensitivity at the level of the kidney, meaning aquaporins in the collecting duct are not activated. It can also result in polyuria and polydipsia.

Lithium is a known iatrogenic cause of nephrogenic diabetes insipidus. Renal function must be monitored regularly in those taking lithium.

Congenital nephrogenic diabetes insipidus can be caused by **a genetic defect in the ADH receptor,** such as AVPR2. This defect results in ADH insensitivity in the kidney.

Haemochromatosis can cause cranial diabetes insipidus, a condition resulting from a deficiency of ADH production from the posterior pituitary which can also present with polyuria. Therefore a history of haemochromatosis would point towards cranial diabetes insipidus rather than primary polydipsia.

Discuss (1) Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

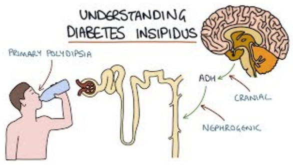
Next question

Textbooks

High-yield textbook

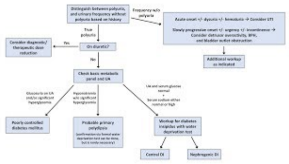
Extended textbook

Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5



An Approach to Polyuria

Strong Medicine - YouTube 👍 29 👎 4

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Score: **30.8%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

PassMedicine

Question 53 of 414 ✗

A 58-year-old man comes for review in the diabetes clinic. He was diagnosed as having type 2 diabetes mellitus (T2DM) around 10 years ago and currently only takes gliclazide and atorvastatin. Three years ago he was successfully treated for bladder cancer. A recent trial of metformin was unsuccessful due to gastrointestinal side-effects. He works as an accountant, is a non-smoker and his BMI is 31 kg/m². His annual bloods show the following:

Na^+	138 mmol/l
K^+	4.1 mmol/l
Urea	4.3 mmol/l
Creatinine	104 µmol/l
HbA1c	62 mmol/mol (7.8%)

What is the most appropriate next step in management?

	Add pioglitazone	9%
🟥	Add exenatide	17%
	Add acarbose	2%
	Add repaglinide	2%
🟩	Add sitagliptin	70%

Pioglitazone is contraindicated by his history of bladder cancer and may contribute to his obesity. A DPP-4 inhibitor such as sitagliptin is therefore the best option.

Exenatide generally causes weight loss and is therefore useful in obese diabetics but he does not meet the NICE body mass index criteria of 35 kg/m².

Discuss (8) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)

Management of T2DM	HbA1c target
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

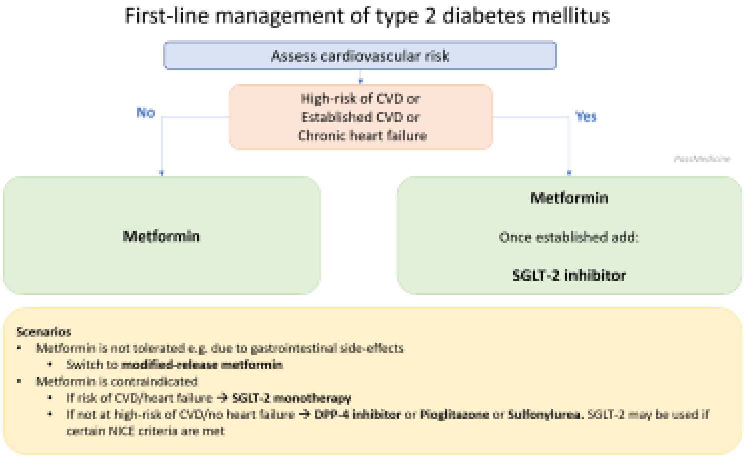
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor
Scenarios
Metformin is not tolerated e.g. due to gastrointestinal side-effects
Switch to modified-release metformin
Metformin is contraindicated
If risk of CVD/heart failure → SGLT-2 monotherapy
If not at high-risk of CVD/no heart failure → DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

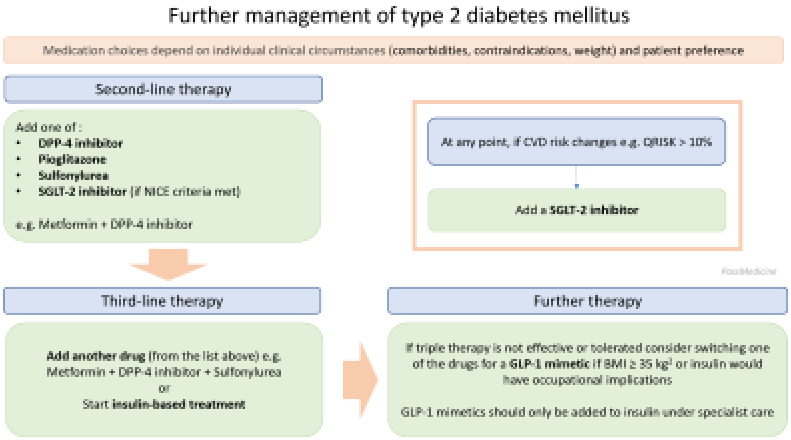
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
• DPP-4 inhibitor
• Pioglitazone
• Sulfonylurea
• SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

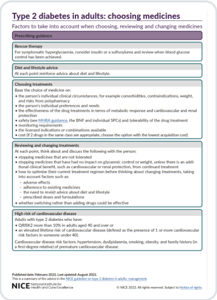
GLP-1 mimetics should only be added to insulin under specialist care

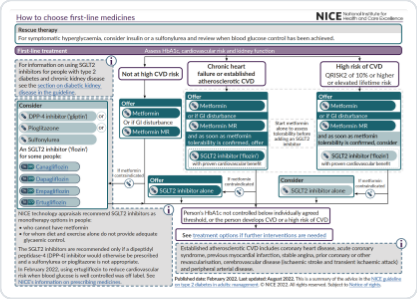
Starting insulin

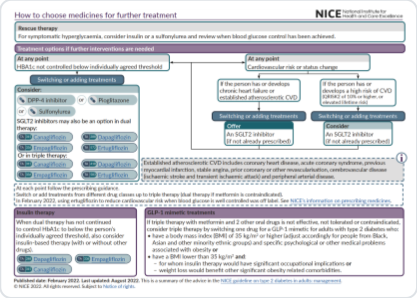
- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

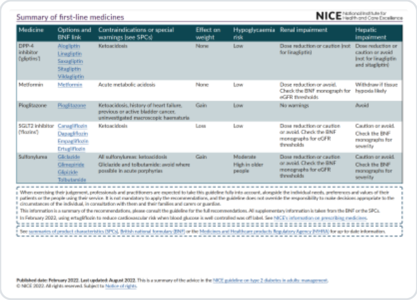
Practical examples

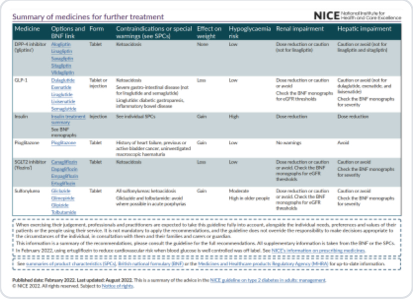
- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea


Type 2 diabetes in adults: choosing medicines


How to choose first-line medicines


How to choose medicines for further treatment


Summary of first-line medicines


Summary of medicines for further treatment

Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

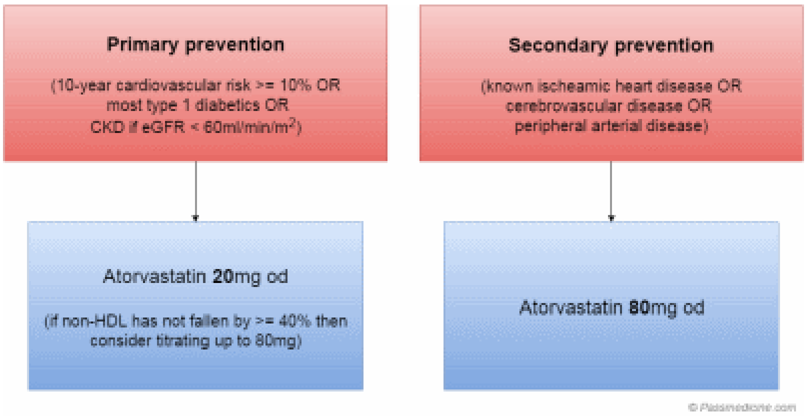
	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

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Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

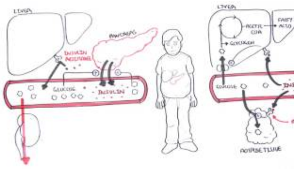
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3

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Question 54 of 414 ✗

A 30-year-old woman who is investigated for obesity, hirsutism and oligomenorrhoea is diagnosed as having polycystic ovarian syndrome (PCOS) following an ultrasound scan. She is hoping to start a family and her doctor starts metformin to try and improve her fertility. What is the mechanism of action of metformin in PCOS?

	Stimulates the release of insulin from the pancreas	3%
	Blocks the insulin mediated development of multiple immature follicles in the ovaries	18%
🟩	Increases peripheral insulin sensitivity	64%
🟥	Blocks the conversion of oestradiol to testosterone	11%
	Increases hepatic gluconeogenesis	4%

The majority of patients with polycystic ovarian syndrome have a degree of insulin resistance which in turn can lead to complicated changes in the hypothalamic-pituitary-ovarian axis.

Discuss (1) Improve

Next question

Polycystic ovarian syndrome: management

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

General

- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne

- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility

- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

Next question

Textbooks

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PassMedicine

Question 55 of 414 ✗

Which one of the following processes is responsible for ketone production during diabetic ketoacidosis?

	Glycogenolysis	10%
	Exchange with hydrogen ions in the collecting ducts	2%
🟥	Gluconeogenesis	10%
	Decreased plasma bicarbonate levels	2%
🟩	Lipolysis	76%

The low-insulin conditions seen in diabetic ketoacidosis stimulate the process of lipolysis and the production of the ketone bodies, beta-hydroxybutyrate and acetoacetate, which can be used as metabolic fuel.

Discuss (5) Improve

Next question

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) may be a complication of existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

Pathophysiology

- DKA is caused by uncontrolled lipolysis (not proteolysis) which results in an excess of free fatty acids that are ultimately converted to ketone bodies

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction.

Features
- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick

Management

Main principles of management
- fluid replacement
  - most patients with DKA are deplete around 5-8 litres
  - isotonic saline is used initially, even if the patient is severely acidotic
  - please see an example fluid regime below.
- insulin
  - an intravenous infusion should be started at 0.1 unit/kg/hour
  - once blood glucose is < 14 mmol/l an infusion of 10% dextrose should be started at 125 mls/hr *in addition* to the 0.9% sodium chloride regime
- correction of electrolyte disturbance
  - serum potassium is often high on admission despite total body potassium being low
  - this often falls quickly following treatment with insulin resulting in hypokalaemia
  - potassium may therefore need to be added to the replacement fluids
  - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- long-acting insulin should be continued, short-acting insulin should be stopped

JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

Fluid	**Volume**
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	**Potassium replacement in mmol/L of infusion solution**
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Resolution

DKA resolution is defined as:

- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

Further points

- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist
- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

Complications

Complications may occur from DKA itself or the treatment:
- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

Next question

Textbooks

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Extended textbook

Links

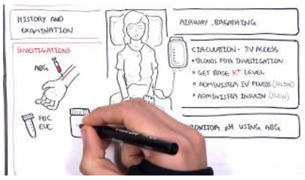
Joint British Inpatient Diabetes Societies Inpatient Care Group

👍 8 👎 4

The Management of Diabetic ketoacidosis in adults

Report broken link

Media


HISTORY AND EXAMINATION
INVESTIGATIONS
ABG
FBC
EUC
AIRWAY, BREATHING
CIRCULATION - IV ACCESS
• BLOODS FOR INVESTIGATION
• GET BASE K+ LEVEL
• ADMINISTER IV FLUIDS (SALINE)
• ADMINISTER INSULIN (SLOW)
MONITOR pH USING ABG

Diabetic Ketoacidosis (Diabetes Type I) Management Summary

Armando Hasudungan - YouTube 👍 14 👎 1

DIABETES MELLITUS
OSMOSIS.org

Diabetes mellitus (type 1, type 2) & diabetic ketoacidosis (DKA) - causes & symptoms

Osmosis - YouTube 👍 7 👎 2

Report broken media

Score: **29.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗

PassMedicine

Question 56 of 414 ✗

A 78-year-old nursing home resident is admitted to the acute medical unit after being found collapsed in his room. A carer from the nursing home is present and reports that he has had regular 'hypos' recently. On admission he was drowsy and the blood glucose was 1.8 mmol/l. Following intravenous dextrose the patient's condition significantly improved.

His medication on admission is as follows:

Metformin 1g bd
Gliclazide 160mg od
Pioglitazone 45mg od
Aspirin 75mg od
Simvastatin 40mg on

What is the most appropriate initial action?

🟥 Stop metformin	1%
Stop pioglitazone	6%
🟩 Stop gliclazide	82%
Make no changes to the medication	1%
Stop all oral antidiabetic medications	10%

Neither metformin nor pioglitazone cause hypoglycaemia. The gliclazide dose is therefore responsible and should be stopped whilst deciding upon longer term changes to his medication.

Discuss (4) | Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015
- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle +	53 mmol/mol

Management of T2DM	HbA1c target
sulfonylurea)	(7.0%)

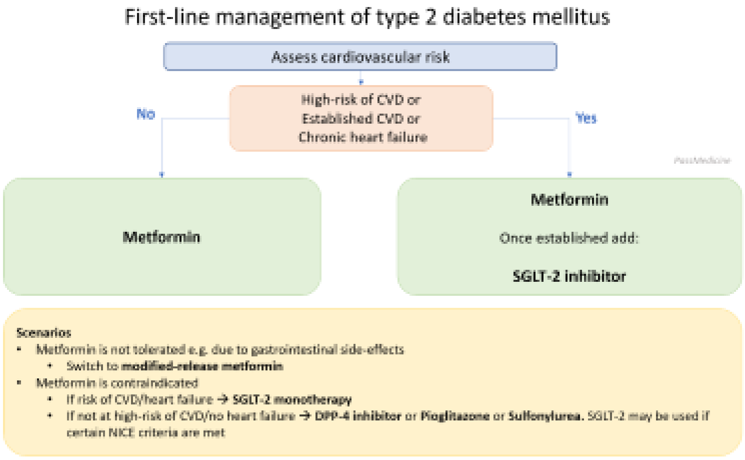
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios

- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors

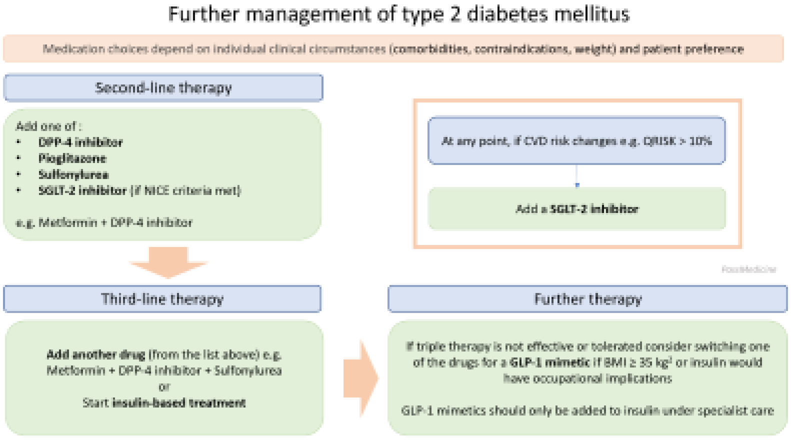
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)

  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
• DPP-4 inhibitor
• Pioglitazone
• Sulfonylurea
• SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care
PassMedicine

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m² and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

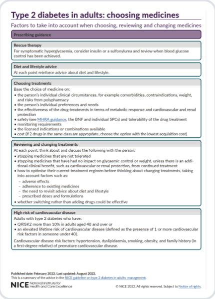
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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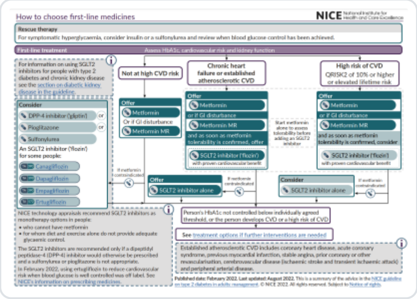

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk

Offer Metformin Or if GI disturbance Metformin MR

Chronic heart failure or established atherosclerotic CVD

Offer Metformin or if GI disturbance Metformin MR and as soon as metformin tolerability is confirmed, offer SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD QRISK2 of 10% or higher or elevated lifetime risk

Offer Metformin or if GI disturbance Metformin MR and as soon as metformin tolerability is confirmed, consider SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated

Consider DPP-4 inhibitor ('gliptin') or Pioglitazone or Sulfonylurea

An SGLT2 inhibitor ('flozin') for some people: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

If metformin contraindicated: Offer SGLT2 inhibitor alone

If metformin contraindicated: Consider SGLT2 inhibitor alone

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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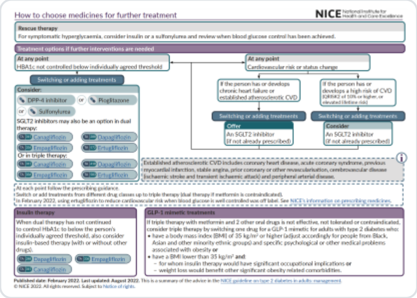

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider: DPP-4 inhibitor or Pioglitazone or Sulfonylurea

SGLT2 inhibitors may also be an option in dual therapy: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

Or in triple therapy: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

At any point Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD

Switching or adding treatments

Offer An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)

Switching or adding treatments

Consider An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

Dapagliflozin, Empagliflozin, Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m² or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m² **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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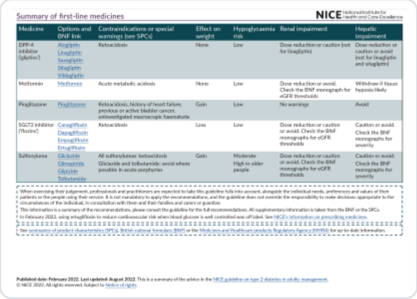

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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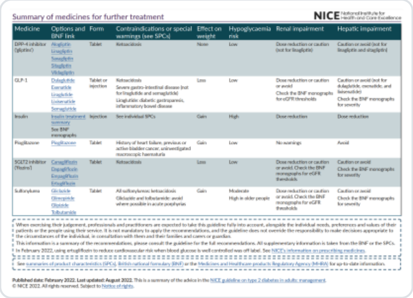

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

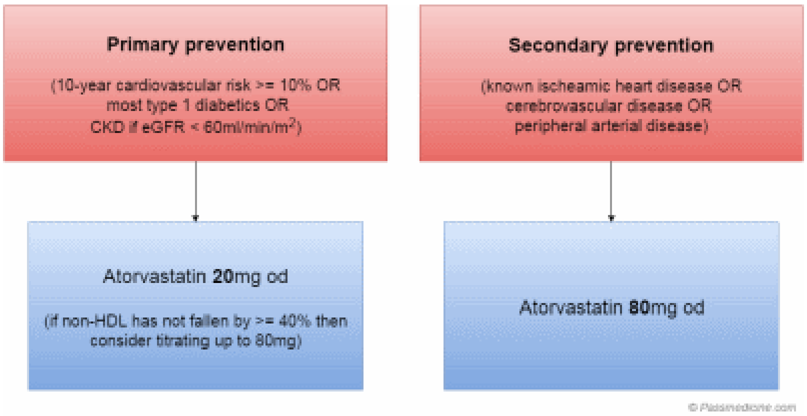
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR
most type 1 diabetics OR
CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischaemic heart disease OR
cerebrovascular disease OR
peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then
consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

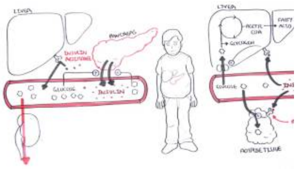
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3

PassMedicine

Question 57 of 414 ✗

You are advising a patient who has recently been diagnosed with chronic kidney disease stage 4 with regards to her diet. Which one of the following foods should she eat in moderation due to the high potassium content?

🟩 Tomatoes	53%
🟥 Plums	7%
Cranberry juice	17%
Grapes	10%
Green beans	13%

The correct answer is **Tomatoes**. Tomatoes are high in potassium, a mineral that can build up in the blood of patients with chronic kidney disease stage 4 as their kidneys' ability to filter it out is compromised. Consuming too much potassium can lead to hyperkalemia, a potentially life-threatening condition characterised by muscle weakness, irregular heart rhythms and, in severe cases, cardiac arrest. Therefore, patients with advanced kidney disease should limit their intake of high-potassium foods like tomatoes.

Plums, on the other hand, are not particularly high in potassium. A medium-sized plum contains around 104 milligrams of potassium, which is relatively low compared to the recommended daily intake for an adult (3,500-4,700 milligrams according to NHS guidelines). Therefore, plums would not need to be eaten in moderation due to potassium content for patients with chronic kidney disease.

Similarly, **Cranberry juice** is also not especially high in potassium. One cup of cranberry juice contains about 200 milligrams of potassium. While this is more than what's found in plums, it's still considered relatively low and unlikely to contribute significantly to hyperkalemia if consumed in moderate amounts.

Grapes are another fruit that's relatively low in potassium. There are approximately 175 milligrams of potassium in one cup of grapes. Like plums and cranberry juice, grapes do not need to be limited due to their potassium content for people with chronic kidney disease.

Finally, **Green beans** contain moderate levels of potassium - around 209 milligrams per half-cup serving - but they're still not as high as tomatoes. Therefore green beans wouldn't necessarily need to be eaten in moderation due specifically to their potassium content by someone with advanced chronic kidney disease.

👍 👎 Discuss (4) Improve

Next question

Hyperkalaemia ★

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia:

- acute kidney injury
- drugs*: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, ciclosporin, heparin**
- metabolic acidosis
- Addison's disease
- rhabdomyolysis
- massive blood transfusion

Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

Next question

Textbooks

High-yield textbook

Extended textbook

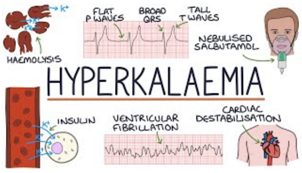
Links

National Kidney Foundation 👍 4 👎 0

Renal Diet

Report broken link

Media


K+
FLAT P WAVES
BROAD QRS
TALL T WAVES
NEBULISED SALBUTAMOL
HAEMOLYSIS
HYPERKALAEMIA
K+
INSULIN
VENTRICULAR FIBRILLATION
CARDIAC DESTABILISATION

Understanding Hyperkalaemia (High Potassium)

Zero To Finals - YouTube 👍 1 👎 0

Hyperkalemia

Osmosis - YouTube 👍 8 👎 1

Report broken media

PassMedicine

← Question 58 of 414 ✗ ⚐ →

A 64-year-old man presents to his GP, concerned about swelling of his chest that seems to have arisen over the past few months, around the nipples. He denies any discharge from the nipples, and otherwise feels generally well in himself. His past medical history includes hypertension, prostate cancer, recurrent nausea, osteoarthritis and depression. His regular medications include amlodipine, goserelin, metoclopramide, naproxen and sertraline.

On examination, bilateral breast tissue is visible and palpable. No discharge is present from the nipples.

Which of his medications is most likely to have caused this presentation?

	Amlodipine	3%
🟩	Goserelin	68%
🟥	Metoclopramide	18%
	Sertraline	6%
	Tamoxifen	4%

GnRH agonists (e.g. goserelin) used in the management of prostate cancer may result in gynaecomastia

Important for me Less important

The correct answer is goserelin. The finding being described here is gynaecomastia - the development of breast tissue in men. Of the drugs listed, the most likely cause is goserelin, a GnRH agonist which this patient is taking for prostate cancer. It is known to cause gynaecomastia. The most common drug cause, however, is spironolactone.

Amlodipine is incorrect. This is a calcium-channel blocker, and there have been a few isolated case reports of an association between these drugs and gynaecomastia, but this is incredibly rare. The most likely cause is still goserelin.

Metoclopramide is a dopamine antagonist used in the management of nausea and vomiting. It is known to cause galactorrhoea - secretion of milk from the nipples - but not gynaecomastia.

Dopamine normally inhibits prolactin, which is responsible for milk secretion, and so antagonising dopamine results in increased prolactin levels.

Sertraline is a selective serotonin reuptake inhibitor, used in the management of depression and anxiety. There are a few case reports of an association with gynaecomastia and galactorrhoea, although this is very rare.

Tamoxifen is a selective oestrogen receptor modulator used to treat breast cancer. Rather than being a cause of gynaecomastia, it can actually be used to treat it. It is licensed for this use (according to the BNF) in patients who are receiving treatment for prostate cancer and develop gynaecomastia as a result of their treatment.

👍 👎 Discuss (1) Improve

Next question

Gynaecomastia ★

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin

- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

Next question

Textbooks

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Extended textbook

Score: **27.6%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

PassMedicine

Question 59 of 414 ✕

A 75-year-old woman with a history of hypothyoidism is admitted to the Emergency Department following an episode of chest pain. She is diagnosed as having an acute coronary syndrome and iron-deficiency anaemia. A percutaneous coronary intervention is performed and a coronary artery stent is inserted. Endoscopies of the upper and lower gastrointestinal tract are performed and reported as normal. She is discharged on the following drugs in addition to her regular levothyroxine: aspirin, clopidogrel, ramipril, lansoprazole, simvastatin and ferrous sulphate. Six weeks later she complains of feeling tired all the time. Her GP arranges some routine blood tests:

Hb	11.9 g/dl
Platelets	155 * 10^9/l
WBC	5.2 * 10^9/l

Free T4	8.1 pmol/l
TSH	8.2 mu/l

Prior to her recent admission the TSH has been within range for the past two years. Which one of the following new drugs most likely explains the raised TSH?

🟥	Simvastatin	10%
	Clopidogrel	4%
🟩	Ferrous sulphate	71%
	Ramipril	4%
	Lansoprazole	10%

Iron / calcium carbonate tablets can reduce the absorption of levothyroxine - should be given 4 hours apart

Important for me Less important

Discuss (3) Improve

Next question

Hypothyroidism: levothyroxine therapy

Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value
- there is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions

- iron, calcium carbonate
  - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 7 👎 6

Management of hypothyroidism

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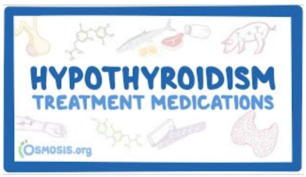
Media


HYPOTHYROIDISM
TREATMENT MEDICATIONS
OSMOSIS.org

Hypothyroidism treatment medications

Osmosis - YouTube 👍 4 👎 1

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Score: **27.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗

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← Question 60 of 414 ✗ ⚐ →

A 43-year-old man requests a 'medical' as he is concerned about his risk of heart disease. His father died at the age of 45-years following a myocardial infarction. His lipid profile is as follows:

HDL	1.4 mmol/l
LDL	5.7 mmol/l
Triglycerides	2.3 mmol/l
Total cholesterol	8.2 mmol/l

Clinical examination reveals tendon xanthomata around his ankles. What is the most likely diagnosis?

🟩	Familial hypercholesterolaemia (heterozygous)	55%
	Nephrotic syndrome	1%
🟥	Mixed hyperlipidaemia	8%
	Familial hypercholesterolaemia (homozygous)	35%
	Hypothyroidism	1%

The presence of tendon xanthomata and cholesterol levels meet the diagnostic criteria for familial hypercholesterolaemia. Homozygous familial hypercholesterolaemia is exceedingly rare - most patients die in their teenage years from a myocardial infarction.

👍 👎 Discuss (2) Improve

Next question

Familial hypercholesterolaemia ★

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Case finding:

- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
    - a total cholesterol level greater than 7.5 mmol/l and/or
    - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:
    - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
    - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Next question

Textbooks

High-yield textbook

Extended textbook

Links

The FH Foundation 👍 3 👎 1

Simon Broom Criteria

The FH Foundation 👍 3 👎 1

High cholesterol during preganancy

NICE 👍 3 👎 1

2008 Familial hypercholesterolaemia guidelines

Public Library of Science (PLoS) 👍 2 👎 1

Cascade Screening for Familial Hypercholesterolemia (FH)

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Media

FAMILIAL
HYPERCHOLESTEROLEMIA
Osmosis.org

Familial hypercholesterolaemia

Osmosis - YouTube 👍 20 👎 1

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PassMedicine

Question 61 of 414 ✗

A 19-year-old man presents to his GP with several months of thirst and frequent urination. He reports several family members experiencing similar symptoms at a similar age, who now take oral medication. The patient is otherwise well and has no past medical history.

Examination is unremarkable; blood tests are taken by the GP which show elevated blood glucose and urinalysis is negative for ketones.

Given the likely diagnosis, the GP commences the patient on gliclazide.

Which of the following is the most common inheritance pattern of this condition?

🟩	Autosomal dominant	77%
	Autosomal recessive	14%
🟥	Mitochondrial	4%
	X-linked dominant	3%
	X-linked recessive	2%

MODY is inherited in an autosomal dominant fashion so a family history is often present

Important for me Less important

The correct answer is autosomal dominant; the diagnosis here is maturity-onset diabetes of the young (MODY). The classic history is that of a patient under 25 years old with diabetic symptoms, no ketosis at presentation and a family history of early-onset diabetes. The other clue in the history is sensitivity to sulfonylureas. It is most commonly inherited in an autosomal dominant fashion.

Autosomal recessive is incorrect. Both parents would have to be carriers for the patient to be exhibiting the condition - an example of this is cystic fibrosis.

With regards to mitochondrial inheritance, mitochondria are inherited from the mother. Any disease of the mitochondrial genetic material can therefore only be passed down from a mother to her children, and only female children will be able to subsequently pass it on to their children.

An example is Leber's hereditary optic neuropathy.

X-linked dominant inheritance is incorrect. A woman with a defective X chromosome will have a 50% chance of passing it on to her children. A male with a defective X chromosome will pass it on to all of his daughters, but none of his sons. An example of an X-linked dominant condition is Fragile X syndrome.

X-linked recessive is incorrect. Men will exhibit these conditions as they only have one X chromosome; women are usually carriers of the disease (unless they, incredibly rarely, have two copies of the defective chromosome, or have Turner's syndrome). Examples include the haemophilias.

👍 👎 Discuss (2) Improve

Next question

MODY ★

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

Textbooks

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← Question 62 of 414 ✗ ⚑ →

A 74-year-old man presents with confusion. He has a 4-week history of vomiting and diarrhoea. He is hypovolaemic on examination.

Blood results are as follows:

Na^+	110 mmol/L	(135 - 145)
K^+	3.6 mmol/L	(3.5 - 5.0)
Urea	6.8 mmol/L	(2.0 - 7.0)
Creatinine	62 µmol/L	(55 - 120)

Osmolarity studies are requested:

Urine osmolarity	85 mmol/L	(300-900)
Urine sodium	14 mmol/L	(> 40)
Plasma osmolarity	240.5 mOsm/kg	(275 - 295)

He receives 2 litres of 0.9% saline over the next 16 hours. He then develops spastic quadriparesis and pseudobulbar palsy. A repeat serum sodium comes back 135 mmol/L.

What is the most likely underlying pathophysiology?

🟩	Astrocyte apoptosis	45%
	Brain stem herniation	13%
🟥	Cerebral haemorrhage	1%
	Cerebral infarction	2%
	Cerebral oedema	38%

Osmotic demyelination syndrome develops secondary to astrocyte apoptosis

Important for me Less important

Astrocyte apoptosis is correct. The patient most likely has hyponatraemia due to excessive gastrointestinal losses. Rapid correction of hyponatremia is a known risk factor for the development of osmotic demyelination syndrome (ODS) which is the most likely complication that has occurred in this case. When osmotic pressure is rapidly increased by the correction of low sodium, a rapid shift in osmolarity leads to dehydration of brain cells, particularly astrocytes, resulting in their injury or death (apoptosis) and subsequent demyelination.

Brain stem herniation is incorrect. Although this remains within the differential diagnosis, the clinical course of rapid deterioration following saline replacement for profound hyponatraemia favours a diagnosis of ODS.

Cerebral haemorrhage is incorrect. Whilst this remains within the differential diagnosis, the clinical features and rapid correction of serum sodium are more in keeping with ODS.

Cerebral infarction is incorrect. The presence of bilateral paralysis makes stroke an unlikely diagnosis.

Cerebral oedema is incorrect. The patient was likely confused initially as a result of cerebral oedema as a consequence of low serum osmolarity. However, the rapid correction of serum osmolarity has then resulted in fluid and electrolyte shifts causing ODS.

👍 👎 Discuss (2) Improve

Next question

Hyponatraemia: treatment

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:

- duration of hyponatremia: is it acute or chronic?
    - acute: develops over a period of < 48 hours
    - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
    - mild: 130-134 mmol/L

    - moderate: 120-129 mmol/L
    - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
    - patients with mild hyponatraemia may be symptomatic
    - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
    - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
    - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
    - euvolemic hyponatraemia: SIADH
    - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected

- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
    - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
    - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider medications:
    - demeclocycline
    - vaptans (see below)

If a hypervolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):

- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia
- pathophysiology:
  - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
  - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

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Question 63 of 414 ✓

A 67-year-old woman presents with lethargy, depression and constipation. A set of screening blood tests reveals the following:

Calcium	3.05 mmol/l
Albumin	41 g/l

What is the single most useful test for determining the cause of her hypercalcaemia?

ESR	1%
Phosphate	4%
Vitamin D level	4%
Parathyroid hormone	90%
ACE level	1%

Parathyroid hormone levels are useful as malignancy and primary hyperparathyroidism are the two most common causes of hypercalcaemia. A parathyroid hormone that is normal or raised suggests primary hyperparathyroidism.

Discuss (6) Improve

Next question

Hypercalcaemia: causes

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
    - PTHrP from the tumour e.g. squamous cell lung cancer
    - bone metastases

  - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include
- sarcoidosis
  - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:
  - thiazides
  - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
  - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

Textbooks

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Links

Royal College of Physicians 👍 9 👎 1

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Question 64 of 414 ✗

A 16-year-old male is reviewed in the endocrinology clinic due to lack of pubertal development. On examination his testes are undescended and there is only scanty pubic hair. What is the most likely diagnosis?

	Down's syndrome	2%
🟩	Kallman's syndrome	42%
	Dubin-Johnson syndrome	2%
	Turner's syndrome	6%
🟥	Klinefelter's syndrome	48%

Cryptorchidism is more suggestive of Kallman's than Klinefelter's syndrome

Discuss (7) | Improve

Next question

Kallmann's syndrome

Kallmann's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallmann's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty.

Features
- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal

- patients are typically of normal or above-average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Management
- testosterone supplementation
- gonadotrophin supplementation may result in sperm production if fertility is desired later in life

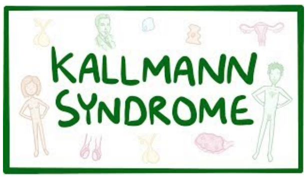
Next question

Textbooks

High-yield textbook

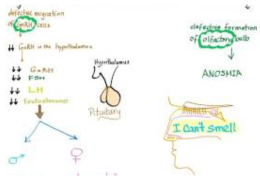
Extended textbook

Media


KALLMANN SYNDROME

Kallman's syndrome

Osmosis - YouTube 42 1


defective migration of GnRH cells
↓↓ GnRH in the hypothalamus
↓↓ GnRH
↓↓ FSH
↓↓ LH
↓↓ testosterone
Hypothalamus
Pituitary
defective formation of olfactory bulb
ANOSMIA
I can't smell

Kallmann Syndrome mnemonic

PassMedicine

Question 65 of 414 ✗

A 55-year-old woman is investigated following an osteoporotic hip fracture. The following results are obtained:

TSH	< 0.05 mu/l
Free T4	29 pmol/l

Which one of the following autoantibodies is most likely to be present?

🟩	TSH receptor stimulating autoantibodies	68%
	Anti-nuclear antibodies	1%
	Anti-thyroglobulin autoantibodies	8%
🟥	Anti-microsomal antibodies	1%
	Anti-thyroid peroxidase autoantibodies	22%

TSH receptor stimulating autoantibodies (often referred to as Thyroid Stimulating Immunoglobulins) are almost diagnostic of Graves' disease, the most common cause of thyrotoxicosis in the UK

Discuss (4) Improve

Next question

Graves' disease: features

Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis

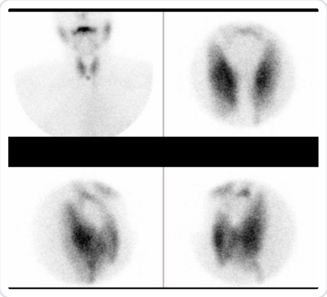
- eye signs (30% of patients)
    - exophthalmos
    - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
    - digital clubbing
    - soft tissue swelling of the hands and feet
    - periosteal new bone formation

Autoantibodies

- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

Thyroid scintigraphy

- diffuse, homogenous, increased uptake of radioactive iodine



Next question

Textbooks

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Question 66 of 414 ✓

A 24-year-old female experiences general weakness, muscle cramps and recurrent renal stones. She is found to be hypertensive and her bloods reveal the following:

Na^+	133 mmol/L	(135 - 145)
K^+	2.6 mmol/L	(3.5 - 5.0)
Bicarbonate	35 mmol/L	(22 - 29)
Urea	7.2 mmol/L	(2.0 - 7.0)
Creatinine	156 µmol/L	(55 - 120)

Calcium	2.3 mmol/L	(2.1-2.6)
Phosphate	0.8 mmol/L	(0.8-1.4)
Magnesium	0.5 mmol/L	(0.7-1.0)

She is diagnosed with a salt-wasting nephropathy named Gitelman's syndrome.

Which channel does the mutation in this condition target?

It targets the sodium-potassium chloride (Na-K-Cl) co-transporter in the loop of Henle	26%
It targets the Na/K antiporter pump in the DCT	14%
It targets the epithelial Na channel in the DCT	7%
[✓ It targets the Na/Cl channel co-transporter in the DCT]	50%
It targets the aquaporin 2 in the collecting duct	4%

Gitelman's syndrome is due to a reabsorptive defect of the NaCl symporter in the DCT

Important for me Less important

Gitelman syndrome is another rare autosomal recessive disorder which occurs due to a mutation causing a resorptive defect of the sodium chloride co-transporter. Its pathogenesis is similar to the mechanism of a thiazide diuretic. It is characterised by hypokalemia-hypomagnesemia and alkaline urine.

Bartter syndrome includes a mutation causing a defect in the Na-K-Cl co-transporter.

Liddle's syndrome includes a mutation causing a defect in epithelial sodium channels located in the DCT.

Aquaporin 2 is controlled by vasopressin. In diabetes insipidus, the kidneys do not respond to aquaporin 2.

The Na/K antiporter pump serves in regulating electrolytes. Disruption of this antiporter is loosely associated with cardiovascular disease, diabetes, neurological disorders and more.

👍 👎 Discuss (16) Improve

Next question

Gitelman's syndrome ★

Gitelman's syndrome is due to a defect in the thiazide-sensitive Na$^+$ Cl- transporter in the distal convoluted tubule.

Features
- normotension
- hypokalaemia
- hypocalciuria
- hypomagnesaemia
- metabolic alkalosis

Next question

B I A T↕

Textbooks

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Question 67 of 414 ✗

A 25-year-old male develops type 2 diabetes mellitus. Which one of the following genes is most likely to be responsible?

	Glucokinase	11%
🟩	HNF-1 alpha	41%
	HNF-4 alpha	24%
🟥	HNF-1 beta	17%
	IPF-1	7%

The correct answer is **HNF-1 alpha**. This gene, also known as Hepatocyte Nuclear Factor 1-alpha, is one of the most common monogenic forms of diabetes, often referred to as MODY (Maturity Onset Diabetes of the Young). Mutations in this gene can lead to an early-onset form of type 2 diabetes, which typically presents in individuals under the age of 25. The disease process involves impaired insulin secretion with minimal or no defects in insulin action.

The other options are less likely for several reasons:

Glucokinase mutations can cause another variant of MODY (specifically MODY2), but this form usually presents with mild hyperglycaemia and is often asymptomatic or mildly symptomatic. It's not typically associated with the development of classic type 2 diabetes mellitus.

HNF-4 alpha mutations result in MODY1, which is a rare cause of monogenic diabetes. Similar to HNF-1 alpha mutations, they lead to early onset type 2 diabetes but are much less common than HNF-1 alpha mutations.

HNF-1 beta, when mutated, leads to MODY5. However, patients with this mutation often present with renal cysts and abnormalities in uterine and genital development along with diabetes. Therefore, it would be less likely in a patient presenting solely with type 2 diabetes mellitus.

Finally, **IPF-1** mutations result in MODY4. These mutations are quite rare and patients usually have exocrine pancreatic insufficiency along with their diabetes due to decreased pancreatic development. Again, this would be atypical for a patient presenting only with type 2 diabetes mellitus.

Discuss (4) Improve

Next question

MODY ★

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of

MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

Textbooks

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Score: **26.9%**

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Question 68 of 414 ×

A 54-year-old man has a routine medical for work. He is asymptomatic and clinical examination is unremarkable. Which of the following results establishes a diagnosis of impaired fasting glucose?

	Fasting glucose 7.1 mmol/L on one occasion	17%
🟩	Fasting glucose 6.8 mmol/L on two occasions	67%
	Glycosuria ++	1%
🟥	75g oral glucose tolerance test 2 hour value of 8.4 mmol/L	10%
	HbA1c of 6.7%	6%

A 75g oral glucose tolerance test 2 hour value of 8.4 mmol/L would imply impaired glucose tolerance rather than impaired fasting glucose

Discuss (5) Improve

Next question

Diabetes mellitus (type 2): diagnosis ★

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic: **CKS**

- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

When HbA1c is used for the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis: CKS

- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

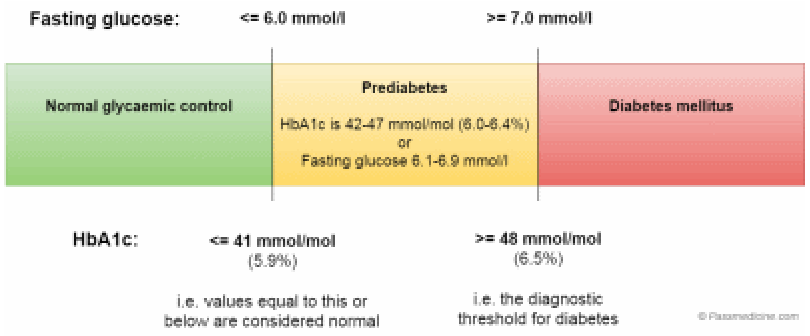
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

Impaired fasting glucose and impaired glucose tolerance

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:

- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Next question

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Links

Clinical Knowledge Summaries 👍 2 👎 1

Type 2 diabetes mellitus: diagnosis

NICE 👍 2 👎 2

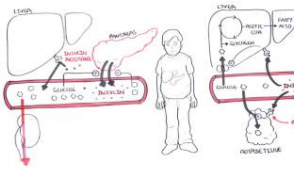
2022 Type 2 diabetes guidelines

Diabetes UK 👍 3 👎 4

New diagnostic criteria for diabetes

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube

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Question 69 of 414 ✓

Which one of the following is not associated with hypocalcaemia combined with a raised phosphate level?

Chronic renal failure	10%
Pseudohypoparathyroidism	19%
Hypoparathyroidism	9%
Osteomalacia	41%
Acute rhabdomyolysis	21%

Osteomalacia causes hypocalcaemia associated with a low serum phosphate, rather than a raised phosphate level.

Discuss (7) Improve

Next question

Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes
- vitamin D deficiency (osteomalacia)
- chronic kidney disease
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion
- acute pancreatitis

Contamination of blood samples with EDTA may also give falsely low calcium levels.

Management

- severe hypocalcaemia (e.g. carpopedal spasm, tetany, seizures or prolonged QT interval) requires IV calcium replacement
  - the preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
  - intravenous calcium chloride is more likely to cause local irritation
  - ECG monitoring is recommended
- further management depends on the underlying cause

Next question

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HYPOCALCEMIA

Hypocalcemia

Osmosis - YouTube 👍 20 👎 4

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Question 70 of 414 ✕

An 18-year-old man presents with polyuria and polydipsia. Observations are as follows: heart rate 85 beats per minute, blood pressure 115/75 mmHg, respiratory rate 16 breaths per minute, temperature 37.2ºC, and oxygen saturation 98% on air.

Blood results are as follows:

Na^+	135 mmol/L	(135 - 145)
K^+	2.8 mmol/L	(3.5 - 5.0)
Bicarbonate	40 mmol/L	(22 - 29)
Urea	7.2 mmol/L	(2.0 - 7.0)
Creatinine	110 µmol/L	(55 - 120)
Serum osmolarity	285 mosmol/kg	(275-295)

Which of the following is defective?

🟥 Aquaporin channels	11%
Epithelial sodium channel	4%
🟩 NKCC2 channel in the ascending loop of Henle	49%
Thiazide-sensitive sodium-chloride cotransporter in the distal convoluted tubule	26%
Thiazide-sensitive sodium-chloride cotransporter in the proximal convoluted tubule	9%

Bartter's syndrome results from a defective NKCC2 channel in the ascending loop of Henle

Important for me Less important

The patient has polyuria, polydipsia and a hypokalaemic alkalosis. Gitelman, Bartter and Liddle syndrome, and liquorice ingestion all cause hypokalaemic alkalosis. These hypokalaemic metabolic alkaloses can be differentiated by blood pressure, age of onset, and serum and urinary biochemistry.

This is a classic case of Bartter's syndrome which presents with polyuria, polydipsia, hypokalemia and a metabolic alkalosis. Whilst Gitelman syndrome remains within the differential diagnosis, the presence of polyuria and polydipsia favour the diagnosis of Bartter's, as these features are not commonly seen in Gitelman. The absence of hypertension makes Liddle syndrome an unlikely diagnosis.

NKCC2 channel in the ascending loop of Henle is correct. This is a classic case of Bartter's syndrome which presents with polyuria, polydipsia, hypokalemia and a metabolic alkalosis. The blood pressure is usually normal in this condition. Bartter's syndrome occurs due to defective chloride absorption at the Na+ K+ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle.

Aquaporin channels is incorrect. Aquaporin channels selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes. Defects in aqua porin channels can result in nephrogenic diabetes insipidus (DI). Although DI remains within the differential, this diagnosis is less likely due to the presence of alkalosis which would be an atypical feature. Furthermore, the normal serum osmolarity is not in keeping with DI which would typically present with plasma hyperosmolality.

Epithelial sodium channel is incorrect. Liddle syndrome is a monogenic form of salt-sensitive hypertension associated with hypokalemia, metabolic alkalosis, suppressed plasma renin activity, and low plasma aldosterone levels. It is caused by gain-of-function mutations in the epithelial sodium channel (ENaC). These patients will present with hypertension making this a less likely diagnosis in this case.

Thiazide-sensitive sodium-chloride cotransporter in the distal convoluted tubule is incorrect. Defects in this channel are associated with Gitelman syndrome. Gitelman syndrome (GS), also referred to as familial hypokalemia-hypomagnesemia, is characterised by hypokalemic metabolic alkalosis in combination with significant hypomagnesemia and low urinary calcium excretion. The blood pressure in these patients if often normal but occasionally low. Whilst this remains within the differential diagnosis, the presence of polyuria and polydipsia favour the diagnosis of Bartter's, as these features are not commonly seen in Gitelman.

Thiazide-sensitive sodium-chloride cotransporter in the proximal convoluted tubule is incorrect. This cotransporter is found in the distal convoluted tubule, but not the proximal.

👍 👎 Discuss (6) Improve

Next question

Bartter's syndrome

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na^+ K^+ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

> Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

Next question

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Links

Royal College of Physicians 👍 9 👎 3

2012 Renal tubular disorders review

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Question 71 of 414 ✗

A 21-year-old with type 1 diabetes was admitted with abdominal pain and vomiting. She had been having dysuria and urine dip showed ++ nitrites and ++ leucocytes. Her heart rate was 90 bpm and blood pressure was 112/80 mmHg. Capillary glucose was 28 mmol/l and capillary ketones were 5.1 mmol/l. A venous gas was obtained which showed:

pH	7.25
Bicarbonate	12 mmol/l
Base excess	-3.8
Lactate	2.9 mmol/l
Potassium	6.0 mmol/l

She was started on IV fluids and fixed-rate IV insulin. Her capillary glucose and ketones had improved significantly after 24 hours of treatment, however she gradually started to become confused, irritable and was slurring her words. A repeat venous gas showed:

pH	7.32
Bicarbonate	17 mmol/l
Base excess	-2.0
Lactate	2.3 mmol/l
Potassium	3.1 mmol/l

What is the most likely cause of her new neurological symptoms?

	Stroke	2%
	Encephalopathy	4%
🟩	Cerebral oedema	75%
🟥	Sepsis	4%
	Hypokalaemia	15%

Cerebral oedema is an important complication of fluid resuscitation in DKA, especially in young patients

Important for me Less important

Children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc.

It usually occurs 4-12 hours following commencement of treatment but can be present at any time.

If any suspicion, request a CT head and call senior immediately.

👍 👎 Discuss (6) Improve

Next question

Diabetic ketoacidosis ★

Diabetic ketoacidosis (DKA) may be a complication of existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

Pathophysiology
- DKA is caused by uncontrolled lipolysis (not proteolysis) which results in an excess of free fatty acids that are ultimately converted to ketone bodies

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction.

Features
- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick

Management

Main principles of management

- fluid replacement
    - most patients with DKA are deplete around 5-8 litres
    - isotonic saline is used initially, even if the patient is severely acidotic
    - please see an example fluid regime below.
- insulin
    - an intravenous infusion should be started at 0.1 unit/kg/hour
    - once blood glucose is < 14 mmol/l an infusion of 10% dextrose should be started at 125 mls/hr *in addition* to the 0.9% sodium chloride regime
- correction of electrolyte disturbance
    - serum potassium is often high on admission despite total body potassium being low
    - this often falls quickly following treatment with insulin resulting in hypokalaemia
    - potassium may therefore need to be added to the replacement fluids
    - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- long-acting insulin should be continued, short-acting insulin should be stopped

JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

Fluid	**Volume**
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours

Fluid	Volume
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Resolution

DKA resolution is defined as:

- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

Further points

- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist
- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

Complications

Complications may occur from DKA itself or the treatment:

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

Next question

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Links

Joint British Inpatient Diabetes Societies Inpatient Care Group 👍 8 👎 4

The Management of Diabetic ketoacidosis in adults

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Media

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Question 72 of 414 ✓

A 24-year-old female is brought into the emergency department with a 3-day history of abdominal pain, vomiting, polyuria and reduced eating and drinking.

She has no past medical history nor is she on any regular medications.

The patient appears unwell with evidence of significant dehydration, a raised respiratory rate and signs of shock. Her observations and venous blood gas (VBG) are shown below.

Obs:

- Heart rate 108 beats per minute
- BP 102/60 mmHg
- Respiratory rate 30/min
- Oxygen saturations 98%
- Temperature 36.7 °C
- Blood glucose 20 mmol/L
- Blood ketones 5 mmol/L

VBG:

pH	7.30	7.35-7.45 nmol/L
pC02	4.3	4.4-5.9 kPa
pO2	6.0	10.0-14.0 kPa
HCO3	14	22-28 mmol/L

Along with an appropriate fluid regime what other management should be started?

IV insulin sliding scale	5%
IV insulin 0.05 unit/kg/hour	4%
[✓ IV insulin 0.1 unit/kg/hour]	77%
IV insulin bolus of 0.15 unit/kg followed by 0.1 unit/kg/hour	13%
Subcutaneous (s/c) insulin bolus of 0.15 unit/kg followed by 0.05 unit/kg/hour	2%

Diabetic ketoacidosis: the IV insulin infusion should be started at 0.1 unit/kg/hour

Important for me Less important

This patient has presented with signs and symptoms in keeping with a new diabetic ketone acidosis (DKA). DKA can be the initial presentation of previously unknown diabetes in patients, often triggered by an acute illness. A diagnosis of DKA is based on the following criteria:

- Glucose >11 mmol/L or known diabetes mellitus
- pH <7.3 nmol/L
- Bicarbonate <15 mmol/L
- Blood ketones >3 mmol/L or urine ketones 2+ on dipstick

Patients presenting in DKA are normally significantly fluid deplete and should be started on a fluid regime of 1L 0.9% sodium chloride over an hour, followed but 2x 1L 0.9% sodium chloride over 2 hours etc. An IV infusion of insulin should also be started at a rate of 0.1 units/kg/hour. If blood glucose falls below 15mmol/L but the patient is still acidotic with ketones then an infusion of 5% dextrose should be started, along with the 0.9% sodium chloride, and insulin continued.

IV insulin sliding scales are no longer recommended for the management of diabetic emergencies. These treatment regimes used to involve adjusting the amount of insulin provided based on the patient's blood glucose level. Fixed-rate insulin infusions are now recommended instead to ensure continued ketone clearance. If a patient's ketone level does not fall by at least 0.5mmol/L/hour or their blood glucose level does not fall by 3mmol/hour then the insulin infusion rate should be increased by 1 unit/hour.

An IV insulin infusion of 0.05 units/kg/hour is the regime recommend in the management of hyperglycaemic hyperosmolar state (HHS). HHS, as the name suggests, is due to hyperglycaemia and high plasma osmolality, however, unlike DKA most HHS patients have enough circulating insulin to prevent ketogenesis and therefore ketonaemia is absent and acidosis is normal mild if present. HHS normally develops over a longer period of time than DKA (several days) and generally affects patients with type 2 diabetes. The main aspect of HHS treatment is fluids with a similar regime as used in DKA. Insulin is generally only started once a patient's blood glucose no longer falls with IV fluids or if there is significant ketonaemia (>1mmol/L or urine ketones>2+). In these cases, an IV insulin infusion of 0.05 units/kg/hour should be started.

IV insulin boluses are no longer recommended regardless of a patient's initial glucose or acidosis level. Insulin boluses have been associated with an increased rate of complications in diabetic emergencies (e.g. cerebral oedema) and therefore should be avoided.

As with IV boluses, s/c insulin boluses should be avoided due to complications. If a patient has an established diagnosis of diabetes and is on an s/c insulin treatment regime then this should be continued along with the management plans discussed above.

👍 👎 Discuss (2) Improve

Next question

Diabetic ketoacidosis ★

Diabetic ketoacidosis (DKA) may be a complication of existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

Pathophysiology
- DKA is caused by uncontrolled lipolysis (not proteolysis) which results in an excess of free fatty acids that are ultimately converted to ketone bodies

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction.

Features
- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick

American Diabetes Association (2009)	Joint British Diabetes Societies (2013)

Management

Main principles of management

- fluid replacement
    - most patients with DKA are deplete around 5-8 litres
    - isotonic saline is used initially, even if the patient is severely acidotic
    - please see an example fluid regime below.
- insulin
    - an intravenous infusion should be started at 0.1 unit/kg/hour
    - once blood glucose is < 14 mmol/l an infusion of 10% dextrose should be started at 125 mls/hr *in addition* to the 0.9% sodium chloride regime
- correction of electrolyte disturbance
    - serum potassium is often high on admission despite total body potassium being low
    - this often falls quickly following treatment with insulin resulting in hypokalaemia
    - potassium may therefore need to be added to the replacement fluids
    - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- long-acting insulin should be continued, short-acting insulin should be stopped

JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

Fluid	Volume
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Resolution

DKA resolution is defined as:

- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

Further points

- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist
- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

Complications

Complications may occur from DKA itself or the treatment:

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
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* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation

in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

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The Management of Diabetic ketoacidosis in adults

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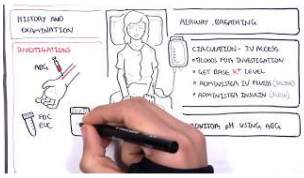
HISTORY AND EXAMINATION
INVESTIGATIONS
AIRWAY, BREATHING
CIRCULATION - IV ACCESS

Diabetic Ketoacidosis (Diabetes Type I) Management Summary

Armando Hasudungan - YouTube 👍 14 👎 1

DIABETES MELLITUS
OSMOSIS.org

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← Question 73 of 414 ✓ →

A 26-year-old woman presents to the emergency department with abdominal pain and vomiting.

She has a past medical history of type 1 diabetes mellitus and is known to be poorly compliant with her insulin therapy.

Her relevant blood results are shown below:

pH	7.31	(7.35-7.45)
Ketones	3.3 mmol/L	(<0.6)
Serum glucose	>30 mmol/L	(4.0-11.1)

What is the most appropriate initial management?

Fixed-rate insulin infusion	11%
IV 0.9% sodium chloride	74%
IV 0.9% sodium chloride with potassium chloride	12%
IV 1.26% sodium bicarbonate	0%
Stat dose of rapid-acting insulin	3%

Diabetic ketoacidosis: isotonic saline should be used initially, even if the patient is severely acidotic

Important for me Less important

IV 0.9% sodium chloride is correct. The priority in treatment is restoring circulatory volume. Sodium chloride is the preferred fluid to achieve this in diabetic ketoacidosis.

Fixed-rate insulin infusion is incorrect. Although fixed-rate insulin infusion forms part of the management, it is only initiated after fluid therapy has begun. Restoring circulatory volume is the priority.

IV 0.9% sodium chloride with potassium chloride is incorrect. The first bag of sodium chloride given does not need to contain potassium chloride. Subsequent bags can have potassium chloride added depending on the patient's serum potassium.

IV 1.26% sodium bicarbonate is incorrect. Sodium bicarbonate is not recommended due to the risk of causing a paradoxical increase in cerebrospinal fluid acidosis. Also, the use of bicarbonate does not reduce ketones as effectively as 0.9% sodium chloride.

Stat dose of rapid-acting insulin is incorrect. Although insulin forms part of the management, it is delivered by fixed-rate insulin infusion.

👍 👎 Discuss (2) Improve

Next question

Diabetic ketoacidosis ★

Diabetic ketoacidosis (DKA) may be a complication of existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

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- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick

Management

Main principles of management

- fluid replacement
    - most patients with DKA are deplete around 5-8 litres
    - isotonic saline is used initially, even if the patient is severely acidotic
    - please see an example fluid regime below.
- insulin
    - an intravenous infusion should be started at 0.1 unit/kg/hour
    - once blood glucose is < 14 mmol/l an infusion of 10% dextrose should be started at 125 mls/hr *in addition* to the 0.9% sodium chloride regime
- correction of electrolyte disturbance
    - serum potassium is often high on admission despite total body potassium being low
    - this often falls quickly following treatment with insulin resulting in hypokalaemia
    - potassium may therefore need to be added to the replacement fluids
    - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- long-acting insulin should be continued, short-acting insulin should be stopped

JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

Fluid	**Volume**
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours

Fluid	Volume
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Resolution

DKA resolution is defined as:

- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

Further points

- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist
- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

Complications

Complications may occur from DKA itself or the treatment:

- gastric stasis

- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

Next question

Textbooks

High-yield textbook

Extended textbook

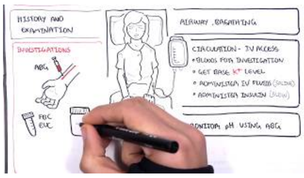
Links

Joint British Inpatient Diabetes Societies Inpatient Care Group 8 4

The Management of Diabetic ketoacidosis in adults

Report broken link

Media


HISTORY AND EXAMINATION
INVESTIGATIONS
ABG
FBC
EUC
AIRWAY, BREATHING
CIRCULATION - IV ACCESS
• BLOODS FOR INVESTIGATION
• GET BASE K+ LEVEL
• ADMINISTER IV FLUIDS (SALINE)
• ADMINISTER INSULIN (SLOW)
MONITOR pH USING ABG

PassMedicine

Question 74 of 414 ✗

A 86-year-old gentleman on a care of the elderly ward he is awaiting social care and is feeling well. The nurses have asked you to review him as he is becoming increasingly confused. His clinical examination is normal. You order some bloods:

Na^+	123 mmol/l
K^+	4.5 mmol/l
Urea	3.6 mmol/l
Creatinine	91 µmol/l

In light of the low sodium, serum and urine osmolalities are ordered. They are as follows:

Plasma osmolality	182 mOsmol/kg	285-295 mOsmol/kg
Urine osmolality	995 mOsmol/kg	500 - 800 mOsmol/kg
Urinary sodium concentration	51 mmol/l	

What is the most appropriate initial treatment?

Oral sodium tablets	3%
Fluid restrict	67%
IV saline	27%
Increased dietary salt	1%
Encourage oral fluids	1%

SIADH is treated with fluid restriction

Important for me Less important

This patient has SIADH, the initial treatment is fluid restriction.

Giving oral or IV salt would not treat his hyponatraemia as it is caused by the dilutionary affect of increased ADH.

Increasing his fluid intake would worsen his hyponatraemia as you would dilute the sodium in his serum even further.

👍 👎 Discuss (14) Improve

Next question

Syndrome of inappropriate ADH secretion

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention. Patients with SIADH are typically euvolemic, i.e. they do not show signs of overt volume depletion or overload.

Pathophysiology

- SIADH involves an excessive release of antidiuretic hormone (ADH), also known as vasopressin, which leads to water retention, volume expansion, and dilutional hyponatraemia
- ADH is produced by the hypothalamus and stored in the posterior pituitary gland. Its primary function is to regulate the body's water balance
- It does this by increasing water reabsorption in the collecting ducts of the kidneys, thereby decreasing the volume of urine produced
- In SIADH, there is an inappropriate and continuous release of ADH that is not inhibited by normal physiological mechanisms, such as adequate or excess body fluid levels
- As a result, the kidneys reabsorb more water, leading to decreased urine output, and expansion of extracellular fluid volume.
- Importantly, this increase in body fluid volume does not lead to the expected signs of fluid overload, such as oedema or hypertension, because the excess fluid is uniformly distributed throughout all body fluid compartments.
- However, as water is retained in the body, the concentration of electrolytes in the blood, particularly sodium, becomes diluted, leading to hyponatraemia.

Causes of SIADH

Category	Examples
Malignancy	**small cell lung cancer** also: pancreas, prostate

Category	Examples
Neurological	stroke subarachnoid haemorrhage subdural haemorrhage meningitis/encephalitis/abscess
Infections	tuberculosis pneumonia
Drugs	sulfonylureas* SSRIs, tricyclics carbamazepine vincristine cyclophosphamide
Other causes	positive end-expiratory pressure (PEEP) porphyrias

Investigations
- Urine osmolality: Urine osmolality is inappropriately high (>100 mOsm/kg) in relation to serum osmolality, as the kidneys should normally dilute urine in the setting of low serum osmolality.
- Urine sodium concentration: Urine sodium concentration is typically high (>40 mmol/L) due to the action of ADH on the renal tubules.

Management
- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

Next question

PassMedicine

Question 75 of 414

The first-line treatment in remnant hyperlipidaemia (dysbetalipoproteinaemia) is:

	Ursodeoxycholic acid	7%
🟥	Vitamin A	4%
	Statins	40%
	Fish oil	7%
🟩	Fibrates	43%

The correct answer is **Fibrates**. Remnant hyperlipidaemia, also known as dysbetalipoproteinaemia or type III hyperlipoproteinaemia, is characterised by increased levels of remnant lipoproteins (chylomicron and VLDL remnants). Fibrates are the first-line treatment for this condition as they act by reducing the production of triglycerides and increasing their clearance. They work by activating peroxisome proliferator-activated receptors (PPARs), particularly PPAR-alpha, which leads to increased lipolysis and elimination of triglyceride-rich particles from plasma. This results in a reduction in the level of circulating remnants.

Ursodeoxycholic acid is not the correct choice because its primary use is in conditions related to bile acids such as primary biliary cholangitis or gallstones. It works by decreasing the production of cholesterol in the liver and altering bile composition, thereby dissolving gallstones. However, it does not have a significant effect on plasma lipid profiles.

Vitamin A is incorrect as it doesn't have a role in managing dyslipidaemias. Vitamin A is necessary for vision, growth, cell division, reproduction and immunity but it doesn't influence lipid metabolism significantly.

The option **Statins** is incorrect because although statins are effective at lowering LDL cholesterol levels, they are not first-line treatment for remnant hyperlipidaemia. Statins inhibit HMG-CoA reductase, an enzyme that plays a central role in the production of cholesterol. However, their effect on triglycerides and remnant lipoproteins is less pronounced compared with fibrates.

Lastly, **Fish oil** supplements contain omega-3 fatty acids which can lower triglyceride levels but they are considered second-line therapy after fibrates according to UK guidelines. While fish oils can be used adjunctively if targets are not met with fibrates alone or if fibrates aren't tolerated well by patients, they shouldn't be used as first-line monotherapy for remnant hyperlipidaemia.

Discuss (5) Improve

Next question

Remnant hyperlipidaemia

Overview

- rare cause of mixed hyperlipidaemia (raised cholesterol and triglyceride levels)
- also known as Fredrickson type III hyperlipidaemia, broad-beta disease and dysbetalipoproteinaemia
- associated with apo-e2 homozygosity
- high incidence of ischaemic heart disease and peripheral vascular disease
- thought to be caused by impaired removal of intermediate density lipoprotein from the circulation by the liver

Features

- yellow palmar creases
- palmer xanthomas
- tuberous xanthomas

Management

- fibrates are first line treatment

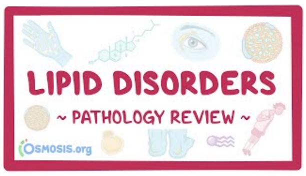
Next question

Textbooks

High-yield textbook

Extended textbook

Media


LIPID DISORDERS
~ PATHOLOGY REVIEW ~
Osmosis.org

Lipid disorders: pathology review

Osmosis - YouTube 👍 20 👎 0

Report broken media

Score: **28%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗
16	✗

PassMedicine

Question 76 of 414 ✕

You review a 47-year-old man one year after he was diagnosed with prediabetes. Last year he had a HbA1c taken after being diagnosed as having hypertension. This was recorded as being 43 mmol/mol (6.1%). His most recent blood test is recorded as being 45 mmol/mol (6.3%) despite the patient reporting that he has changed his diet as instructed and exercising three times a week. His body mass index (BMI) today is 26.5 kg/m^2. Last year it was 27.5kg/m^2. What is the most appropriate course of action?

🟩	Start metformin	50%
	Start pioglitazone	1%
	Review again in 12 months	24%
🟥	Start orlitstat	2%
	Do a oral glucose tolerance test	24%

NICE recommend metformin for adults at high risk '*whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme*'.

Discuss (13) Improve

Next question

Prediabetes and impaired glucose regulation

Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. The term includes patients who have been labelled as having either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes. Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.

Terminology

- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

Identification of patients with prediabetes

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

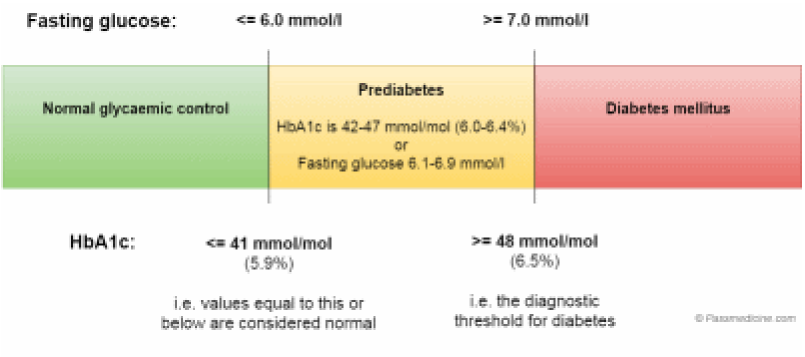

Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
© Passmedicine.com

Diagram showing the spectrum of diabetes diagnosis

Management

- lifestyle modification: weight loss, increased exercise, change in diet
- at least yearly follow-up with blood tests is recommended
- NICE recommend metformin for adults at high risk '*whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme*'

Impaired fasting glucose and impaired glucose tolerance

There are two main types of IGR:

- impaired fasting glucose (IFG) - due to hepatic insulin resistance
- impaired glucose tolerance (IGT) - due to muscle insulin resistance
- patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Definitions

- a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)
- impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- people with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 2

2012 Preventing type 2 diabetes guidelines

Report broken link

Score: **27.6%**

1 ✓
2 ✓

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Question 77 of 414 ✗

A woman presents to her GP with a painful neck, rapid heartbeat, palpitations and feeling warm. A couple of weeks ago, she experienced general malaise and fever and suspected she had influenza - this has since resolved. She is otherwise healthy and takes no regular medications.

On examination, she is tachycardic. A goitre is palpable in the neck and elicits pain when examined. Blood tests are taken:

Thyroid-stimulating hormone (TSH)	0.08 mU/L	(0.5-5.5)
Free thyroxine (T4)	26 pmol/L	(9.0 - 18)
Erythrocyte sedimentation rate	56 mm/hr	(1 - 20)

Which of the following is the most appropriate management, given the likely diagnosis?

	Carbimazole	23%
🟥	Carbimazole and levothyroxine	9%
🟩	Naproxen	52%
	Propylthiouracil	10%
	Radioiodine	6%

Thyrotoxicosis with tender goitre = subacute (De Quervain's) thyroiditis

Important for me Less important

The correct answer is naproxen. The diagnosis here is that of subacute (De Quervain's) thyroiditis, given the history of following a viral illness, raised ESR, tender goitre and initial hyperthyroid phase. Ultimately, this condition is usually self-limiting, and simple analgesia is all that is required.

Carbimazole is incorrect. Symptoms are due to the release of the preformed hormone, and so carbimazole will be ineffective as inhibiting new hormone synthesis will not prevent symptoms.

Similarly, a block-and-replace regime of carbimazole and levothyroxine will thus be ineffective. The preformed hormone is being released, causing symptoms.

Propylthiouracil would be a suitable alternative to carbimazole as an antithyroid medication. Again, however, this would be ineffective in subacute thyroiditis.

Radioiodine would also be unnecessary - subacute thyroiditis is generally self-limiting and so simple analgesia is usually all that is needed.

👍 👎 Discuss (1) Improve

Next question

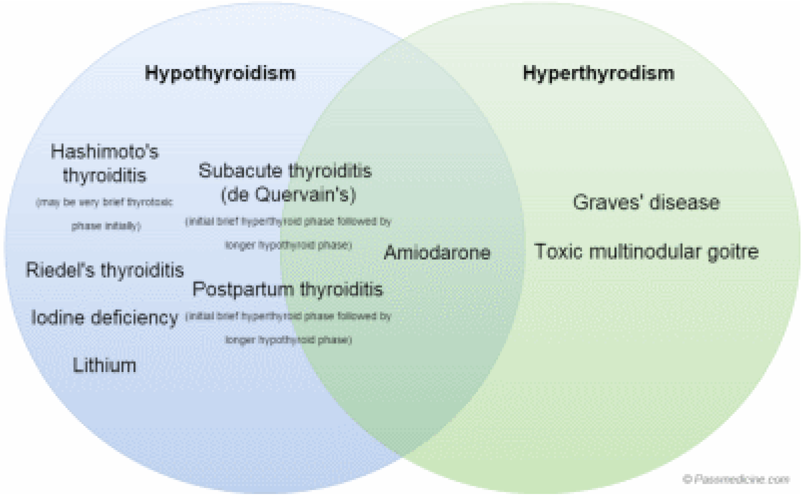
Subacute (De Quervain's) thyroiditis ★

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

Investigations
- thyroid scintigraphy: globally reduced uptake of iodine-131

Management
- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Graves' disease
Amiodarone
Toxic multinodular goitre
Riedel's thyroiditis
Postpartum thyroiditis
Iodine deficiency
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Lithium
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

Textbooks

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Extended textbook

Score: **27.3%**

1 ✓
2 ✓
3 ✓
4 ✗

PassMedicine

Question 78 of 414 ✗

A 62-year-old woman presents to her general practitioner with several weeks of polyuria and polydipsia. She has a background of COPD, ischaemic heart disease, hypertension and previous myocardial infarction. Examination is unremarkable and observations are normal. She is referred for blood tests, which show an HbA1c of 66 mmol/mol.

After being commenced on metformin, she experiences significant gastrointestinal upset. This is changed to the modified-release formulation, but she does not tolerate this either.

What is the next most appropriate treatment for this patient?

🟩	Empagliflozin	68%
	Gliclazide	16%
	Insulin glargine	2%
🟥	Linagliptin	12%
	Pioglitazone	3%

T2DM initial therapy: if metformin is contraindicated + patient has a risk of CVD, established CVD or chronic heart failure → SGLT-2 monotherapy

Important for me Less important

Management of type 2 diabetes mellitus can be quite complex at times, with a variety of drug classes used, each with its own side effects and contraindications. For most people, the modified-release formulation of metformin will be tolerated if standard metformin was not. However, for people who do not tolerate this either, the next choice of monotherapy partly depends on their comorbidities. For patients with suspected or established heart failure or cardiovascular disease, the first choice is a sodium-glucose co-transporter 2 (SGLT2) inhibitor, such as **empagliflozin**. Evidence suggests that these drugs have a beneficial effect on these comorbidities. As this patient has a history of ischaemic heart disease and myocardial infarction, this is the most appropriate choice. It would also be used as an adjunct to metformin if metformin was tolerated but inadequate alone.

Gliclazide, a sulfonylurea, is often used second-line if metformin is not tolerated. However, in the context of the patient's heart failure, empagliflozin is preferable due to it being an SGLT2 inhibitor.

Insulin glargine may be used further down the line to control type 2 diabetes mellitus if a number of oral medications have been tried and have been unsuccessful.

Linagliptin is a dipeptidyl peptidase 4 and may also be used as monotherapy if metformin has not been tolerated. However, in the context of heart failure, an SGLT2 inhibitor is preferable.

Pioglitazone is a thiazolidinedione and may be used initially as monotherapy if metformin was not tolerated. However, it is contraindicated in patients with heart failure due to its risk of inducing fluid retention.

👍 👎 Discuss (2) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

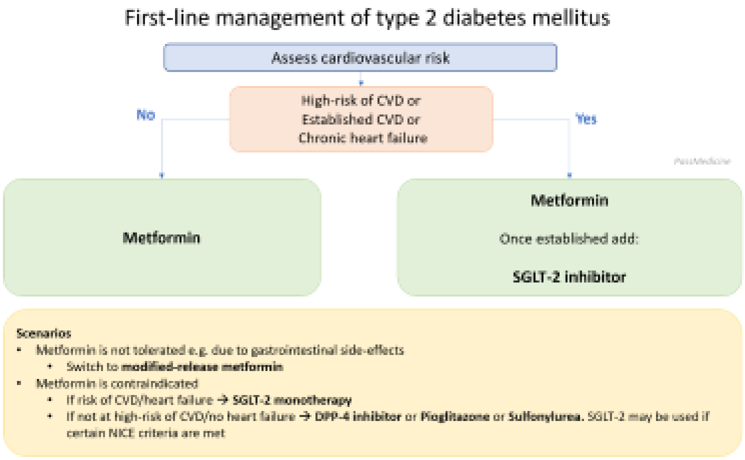
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or
Established CVD or
Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios
- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

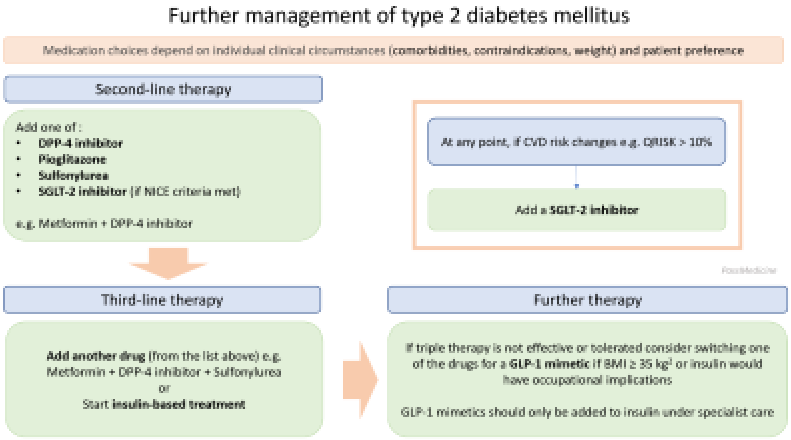
Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.
- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated
- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

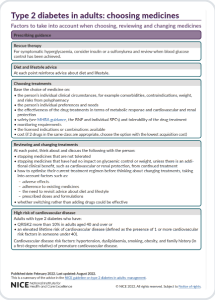
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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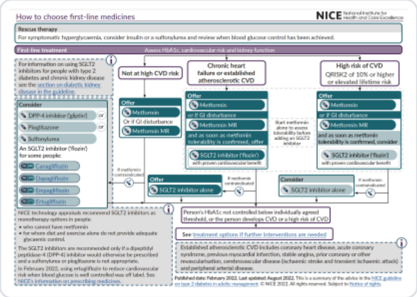

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk
Chronic heart failure or established atherosclerotic CVD
High risk of CVD QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
Or if GI disturbance
Metformin MR
or if GI disturbance
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit
Start metformin alone to assess tolerability before adding an SGLT2 inhibitor
and as soon as metformin tolerability is confirmed, consider
Consider
DPP-4 inhibitor ('gliptin')
or
Pioglitazone
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
If metformin contraindicated
SGLT2 inhibitor alone

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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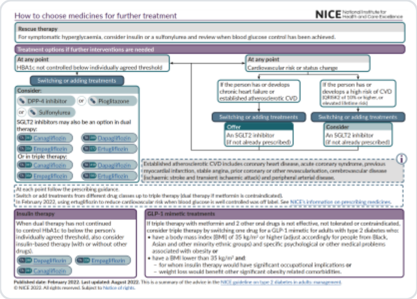

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold
At any point
Cardiovascular risk or status change
Switching or adding treatments
Consider:
DPP-4 inhibitor
or
Pioglitazone
or
Sulfonylurea
If the person has or develops chronic heart failure or established atherosclerotic CVD
If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

SGLT2 inhibitors may also be an option in dual therapy:

Or in triple therapy:

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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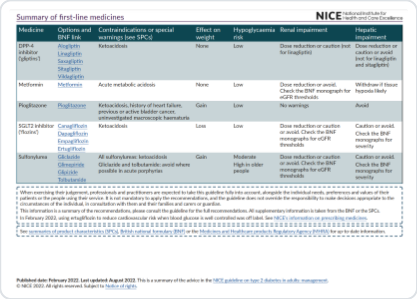

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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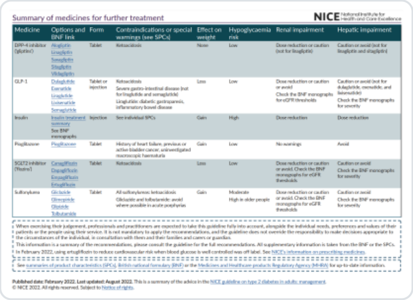

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

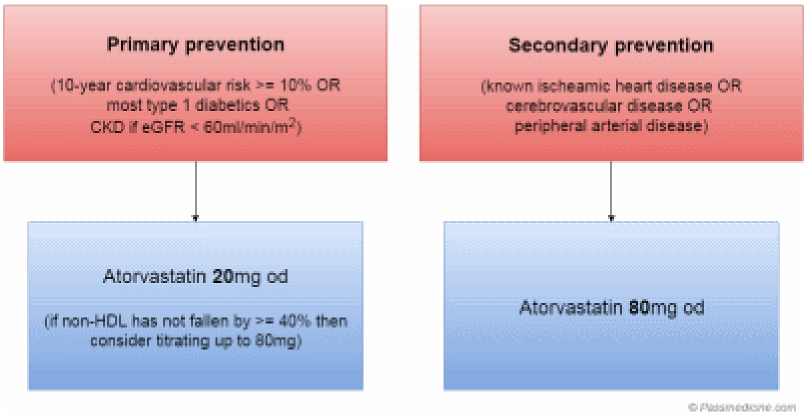
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

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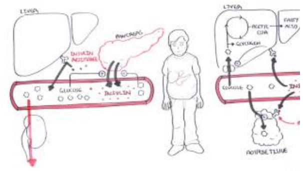
Media

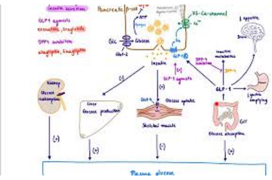


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

Report broken media

Score: **26.9%**

1 ✓

2 ✓

3 ✓

PassMedicine

Question 79 of 414 ✗

Which one of the following statements regarding dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes mellitus is correct?

	Metformin should always be co-prescribed	9%
🟩	Do not cause weight gain	72%
🟥	Is given via a subcutaneous injection	5%
	An example is exenatide	6%
	Patients should be warned that hypoglycaemia is the most common side-effect	8%

The correct answer is '**Do not cause weight gain**'. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, are oral antidiabetic drugs used in the management of type 2 diabetes mellitus. One of their key characteristics is that they do not lead to weight gain, unlike some other antidiabetic medications. This makes them a suitable choice for patients who are overweight or obese.

The first option '**Metformin should always be co-prescribed**' is incorrect. While it's true that metformin is often the first-line treatment for type 2 diabetes and can be used in combination with DPP-4 inhibitors, it's not mandatory to co-prescribe these two medications. The decision depends on individual patient factors and the severity of their condition.

'**Is given via a subcutaneous injection**' is also false. DPP-4 inhibitors are administered orally, which makes them more convenient for many patients compared to injectable antidiabetic drugs.

The statement '**An example is exenatide**' isn't accurate either. Exenatide belongs to a different class of drugs known as glucagon-like peptide-1 (GLP-1) agonists, which are indeed administered via subcutaneous injections.

Finally, the claim that '**Patients should be warned that hypoglycaemia is the most common side-effect**' isn't true. While hypoglycaemia can occur when using DPP-4 inhibitors, especially if combined with sulfonylureas or insulin, it's not the most common side effect. These drugs have a low risk of hypoglycaemia when used alone because they act by increasing insulin secretion in a glucose-dependent manner. The most common side effects include upper respiratory tract infections and headaches.

👍 👎 Discuss (2) Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
>
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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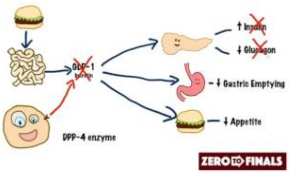
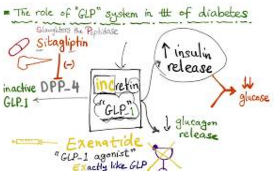
Media


GLP-1
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

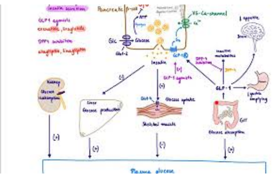
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2


The role of "GLP" system in tt of diabetes
Sitagliptin
(-)
inactive DPP-4
GLP-1
incretin
"GLP-1"
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 26 👎 5

PassMedicine

Question 80 of 414 ✗

A 53-year-old woman presents to her general practitioner complaining of weakness, sweating and tremor. She has no past medical history.

On examination, there is a fine tremor of her outstretched hands. There is proximal weakness with power measured at 4/5 at shoulder abduction and hip flexion. Ocular examination reveals proptosis and chemosis bilaterally. There is waxy discoloured skin on her shins.

Given the likely diagnosis, which antibody is most likely to be positive?

	Anti-MuSK antibodies	3%
🟩	Anti-TSH receptor antibodies	64%
🟥	Anti-acetylcholine receptor antibodies	4%
	Anti-thyroglobulin antibodies	6%
	Anti-thyroid peroxidase (TPO) antibodies	23%

TSH antibodies are found in 90% of patients with Graves' disease and can help distinguish from other forms of hyperthyroidism

Important for me Less important

Anti-TSH receptor antibodies is the correct answer. The patient reports tremors, weakness and sweating. The examination reveals proptosis, chemosis and likely pretibial myxoedema (waxy discolouration of the lower limbs). These findings point to a diagnosis of Graves' disease. TSH antibodies are found in 90% of patients with Graves' disease and can help distinguish from other forms of hyperthyroidism

Anti-MuSK antibodies is not the right answer. This antibody is associated with generalized myasthenia gravis. While this could cause weakness, it would not explain the rash or tremor. Additionally, these antibodies are less likely to be found in the ocular myasthenia subtype.

Anti-acetylcholine receptor antibodies is not the right answer. This antibody is associated with myasthenia gravis. This can cause weakness and eye signs. However, the weakness tends to be fatigable and the eye signs are more likely to be ptosis and ophthalmoplegia rather than chemosis and proptosis. It would not explain the rash or the tremor or the sweating.

Anti-thyroglobulin antibodies is not the right answer. These can be present in hypo or hyperthyroid patients but are present in only 30% of patients with Graves' disease.

Anti-thyroid peroxidase (TPO) antibodies is not the right answer. These are present in approximately 75% of Graves' disease patients.

👍 👎 Discuss (5) Improve

Next question

Graves' disease: features ★

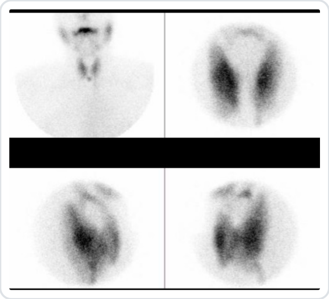
Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis
- eye signs (30% of patients)
  - exophthalmos
  - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
  - digital clubbing
  - soft tissue swelling of the hands and feet
  - periosteal new bone formation

Autoantibodies
- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

Thyroid scintigraphy
- diffuse, homogenous, increased uptake of radioactive iodine



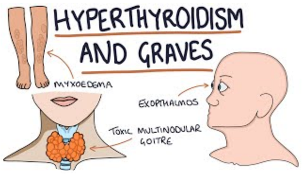
Next question

Textbooks

High-yield textbook

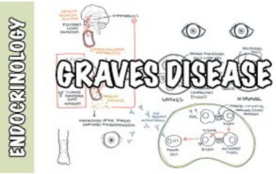
Extended textbook

Media


HYPERTHYROIDISM AND GRAVES
MYXOEDEMA
EXOPTHALMOS
TOXIC MULTINODULAR GOITRE

Understanding Hyperthyroidism and Graves' Disease

Zero to Finals - YouTube 👍 25 👎 2


ENDOCRINOLOGY
GRAVES DISEASE

Graves' disease

Armando Hasudungan - YouTube 👍 14 👎 3

Report broken media

PassMedicine

Question 81 of 414 ✗

A 54-year-old woman has been referred to your endocrinology clinic due to low sodium levels.

She has a background of recurrent urinary tract infections and drinks 4 litres of water per day to reduce the frequency.

Na^+	123 mmol/L	(135 - 145)
K^+	3.5 mmol/L	(3.5 - 5.0)
Urea	3.2 mmol/L	(2.0 - 7.0)
Creatinine	55 µmol/L	(55 - 120)
Serum osmolality	275 mosmol/kg	(285-295)
Cortisol	455 nmol/L	(140-690)
TSH	3.4 mU/L	(0.45 - 4.5)

You arrange a water deprivation test. What are the results most likely to show?

Urine osmolality high after fluid deprivation AND after desmopressin	65%
Urine osmolality high after fluid deprivation but low after desmopressin	8%
Urine osmolality low after fluid deprivation AND after desmopressin	9%
Urine osmolality low after fluid deprivation but high after desmopressin	6%
Urine osmolality normal after fluid deprivation and normal after desmopressin	12%

Water deprivation test: primary polydipsia

- urine osmolality after fluid deprivation: high
- urine osmolality after desmopressin: high

Important for me Less important

The water deprivation test involves preventing the patient from drinking water for up to eight hours and measuring serial urine and serum osmolalities. A high osmolality indicates high concentration (i.e. there are more 'particles' per unit volume) and a low osmolality indicates a dilute solution (i.e. there are fewer 'particles' per unit volume).

Patients with primary polydipsia generally have dilute serum and dilute urine prior to the test caused by the high fluid intake and resultant high fluid output.

Urine osmolality high after fluid deprivation AND after desmopressin is correct. If a patient with primary polydipsia is prevented from drinking water the serum osmolality rises, the kidneys then hold onto water in response and concentrate the urine giving a raised urine osmolality. Equally, if this same patient is given desmopressin (a vasopressin analogue), the structurally normal kidneys response is to conserve water, causing increased urine osmolality.

Urine osmolality high after fluid deprivation but low after desmopressin is incorrect. This would not be physiologically possible unless the test was done incorrectly e.g. if the patient began drinking excessively after desmopressin was administered.

Urine osmolality low after fluid deprivation but high after desmopressin is incorrect, this is the picture you would see in cranial diabetes insipidus. In cranial diabetes insipidus there is a lack of vasopressin production. Because of this, when the patient undergoes water deprivation they are not able to instruct the kidneys to hold onto water in response to rising serum osmolality, this means they have a low urine osmolality despite water deprivation. When desmopressin is administered the kidneys have a normal response to this and conserve water, thus leading to a rise in urine osmolality.

Urine osmolality low after fluid deprivation AND after desmopressin is incorrect. This would be seen in nephrogenic diabetes insipidus as the kidneys are unable to respond to the desmopressin and so do not receive the message to retain water.

Urine osmolality normal after fluid deprivation and normal after desmopressin is incorrect. This could be seen in a partial nephrogenic diabetes insipidus.

👍 👎 Discuss (3) Improve

Next question

Water deprivation test ★

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method

- prevent patient drinking water
- ask the patient to empty their bladder

- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

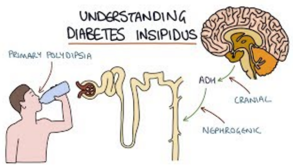
Next question

Textbooks

High-yield textbook

Extended textbook

Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5

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Question 82 of 414 ✕

A 44-year-old woman presents to her GP with polydipsia and polyuria.

The GP arranges a water deprivation test. Blood results before the test show:

Serum osmolality	262 mOsmol/kg	(275 - 295)
Urine osmolality	98 mOsmol/kg	

The test starts at 8 AM and the patient has no fluid intake for the next 8 hours.

After 8 hours, urine osmolality is measured:

Urine osmolality	833 mOsmol/kg

Desmopressin is then given intramuscularly. After 4 hours the urine osmolality is measured again:

Urine osmolality	835 mOsmol/kg

What is the most accurate interpretation of these results?

	Cranial diabetes insipidus	13%
	Diabetes mellitus	1%
	Nephrogenic diabetes insipidus	26%
🟥	Normal study	8%
🟩	Primary polydipsia	52%

Water deprivation test: primary polydipsia

- urine osmolality after fluid deprivation: high
- urine osmolality after desmopressin: high

Important for me Less important

Primary polydipsia is correct. In primary polydipsia, the patient drinks excessive amounts of water, causing dilution of the serum and urine, leading to low serum osmolality and low urine osmolality. Following water deprivation, the urine becomes more concentrated, and osmolality rises to >750mOsmol/kg. Realistically, it would not be necessary to continue to desmopressin in this instance. If the urine osmolality rises to >600mOsmol/kg following fluid deprivation, the test can be stopped as diabetes insipidus has been excluded, because the kidneys are obviously able to concentrate the urine appropriately in response to endogenous antidiuretic hormone.

Cranial diabetes insipidus is incorrect. In cranial diabetes insipidus, the body is incapable of producing any antidiuretic hormone. As a result, the urine would not concentrate and the urine osmolality would not increase in response to water deprivation. Following injection of desmopressin, however, the kidneys would then suddenly be able to concentrate the urine, and we would see a sudden rise in the urine osmolality.

Diabetes mellitus is incorrect. The water deprivation test is not used to diagnose diabetes mellitus.

Nephrogenic diabetes insipidus is incorrect. In nephrogenic diabetes insipidus, the kidneys cannot respond to the antidiuretic hormone and therefore cannot concentrate the urine; the urine will be diluted. Urine osmolality will be low and will remain low after water deprivation and after desmopressin injection.

Normal study is incorrect. In a normal study, the initial serum and urine osmolalities should be within the normal ranges. Following water deprivation, urine osmolality should increase. The test can then be stopped without progressing to desmopressin as diabetes insipidus has been excluded. The initial low serum and urine osmolalities point away from a normal study and suggest primary polydipsia instead.

👍 👎 Discuss (3) Improve

Next question

Water deprivation test ★

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method

- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

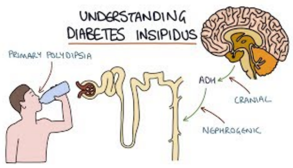
Next question

Textbooks

High-yield textbook

Extended textbook

Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

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Question 83 of 414 ✗

A 22-year-old man was diagnosed with diabetes mellitus 2 years ago after presenting with weight loss, polyuria and polydipsia.

He was initially commenced on insulin therapy, but after further investigations, he was eventually found to have a mutation in his HNF4α gene and was subsequently diagnosed with maturity-onset diabetes of the young (MODY) type 1.

He has therefore between switched to an oral anti-diabetic agent which has maintained good glycaemic control for the past 12 months.

What is the mechanism of the drug that he has most likely been given?

	Activation of peroxisome proliferator-activated receptor-gamma	5%
	Inhibition of hepatic glucose production and increased peripheral glucose uptake in skeletal muscle	25%
🟩	Binding to ATP-dependent K+ channel on the pancreatic beta cell membrane	63%
🟥	Inhibition of intestinal alpha-glucosidase	2%
	Inhibition of dipeptidyl peptidase-4	6%

Sulfonylureas - bind to an ATP-dependent K$^+$(K$_{ATP}$) channel on the cell membrane of pancreatic beta cells

Important for me Less important

This patient has most likely been commenced on a sulphonylurea. These drugs promote endogenous pancreatic insulin secretion by binding to ATP-dependent K+ channel on the pancreatic beta-cell membrane. This is recommended as the first-line pharmacological treatment in patients with MODY type 1, where the underlying genetic defect results in reduced endogenous insulin secretion.

Activation of peroxisome proliferator-activated receptor-gamma (PPARÎ³) describes the action of thiazolidinediones (glitazones), which are not usually used in this population.

Inhibition of hepatic glucose production, and increased peripheral uptake, refers to metformin (biguanide class). The precise mechanism of this drug has still not been fully elucidated, but it is well known to inhibit hepatic glucose production and stimulate peripheral glucose uptake. It has been shown to be inferior to sulphonylureas in MODY type 1.

Inhibition of intestinal alpha-glucosidase describes the effect of acarbose. It is not used in patients with MODY.

Dipeptidyl peptidase-4 inhibitors (gliptins) are commonly used in type 2 diabetes, but not first-line treatment in MODY.

👍 👎 Discuss (1) Improve

Next question

Sulfonylureas ★

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

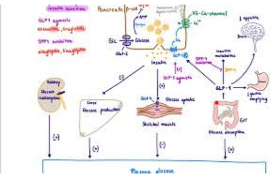
Next question

Textbooks

High-yield textbook

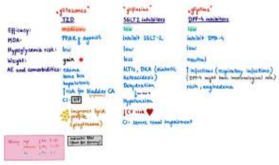
Extended textbook

Media



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10



Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

Report broken media

Score: **25.3%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗

PassMedicine

← Question 84 of 414 ✓ →

Dynamic pituitary function tests may be used to assess each one of the following, except:

Cortisol	26%
Prolactin	14%
Growth hormone	7%
Follicular stimulating hormone	9%
Antidiuretic hormone	45%

Discuss (7) Improve

Next question

Dynamic pituitary function tests ★

A dynamic pituitary function test is used to assess patients with suspected primary pituitary dysfunction

Insulin, TRH and LHRH are given to the patient following which the serum glucose, cortisol, growth hormone, TSH, LH and FSH levels are recorded at regular intervals. Prolactin levels are also sometimes measured*

A normal dynamic pituitary function test has the following characteristics:

- GH level rises > 20mu/l
- cortisol level rises > 550 mmol/l
- TSH level rises by > 2 mu/l from baseline level
- LH and FSH should double

*dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinaemia. A normal response is at least a twofold rise in prolactin. A blunted prolactin response suggests a prolactinoma

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **26.2%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗
12 ✓
13 ✗
14 ✓
15 ✗

PassMedicine

Question 85 of 414 ✓

A 55-year-old man presents for his diabetes check-up. He is currently taking metformin 1g twice daily.

His HbA1c on review is 61mmol/mol.

His BMI is 36 kg/m^2 and he requests that any new medications started will not cause him any further weight gain.

What medication should be avoided?

Canagliflozin	8%
Exenatide	10%
Gliclazide	60%
Liraglutide	5%
Vildagliptin	17%

Sulfonylureas often cause weight gain

Important for me Less important

This question focuses on choosing a diabetic medication that does not have a side effect of weight gain.

Gliclazide is a medication in the sulfonylurea class. The sulfonylureas have the negative side effect of causing weight gain.

Canagliflozin is a medication in the sodium-glucose co-transporter-2 (SGLT2)- inhibitor group. These medications cause weight loss, via the excretion of glucose by the kidneys.

Exenatide and liraglutide are medications in the Glucagon-like peptide-1 (GLP1)-agonist group. They are administered subcutaneously and help with weight loss. They are used for patients who are overweight and who meet specific other criteria. Liraglutide has the added benefit of being given only once a day.

Vildagliptin is a Dipeptidyl-peptidase 4 (DPP4)-inhibitor that works by increasing levels of incretins. DPP-4 inhibitors do not cause weight gain.

Discuss (1) Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

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- weight gain

Rarer adverse effects

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- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

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Textbooks

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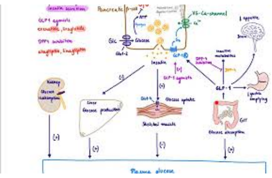
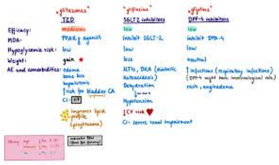


Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10



Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

Report broken media

Score: **27.1%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗

A 56-year-old man attends the clinic for a diabetes review. He has a history of type 2 diabetes mellitus managed with metformin 1 g twice daily, gliclazide 160 mg twice daily, and linagliptin 5 mg once daily.

Over the past six months, he has gained weight and his current BMI is 42 kg/m^2. His glycated haemoglobin (HbA1c) level is 83 mmol/mol, and he has developed mild peripheral sensory neuropathy in his feet.

In accordance with the clinical guidelines, he has been switched to a new medication.

What is the mechanism of action of this new medication?

	ATP-sensitive potassium channel inhibitor	4%
	DPP-4 inhibitor	12%
🟩	GLP1 agonist	63%
	PPAR-gamma activator	3%
🟥	SGLT-2 inhibitor	18%

TD2M: if a triple combination of drugs has failed to reduce HbA1c then switching one of the drugs for a GLP-1 mimetic is recommended, particularly if the BMI > 35

Important for me Less important

The patient presents with a BMI exceeding 35 kg/m^2 and suboptimal glycaemic control despite treatment with three oral hypoglycaemic agents: metformin, gliclazide, and linagliptin. In this context, the introduction of a GLP-1 agonist is a logical next step in their management plan. Liraglutide, a **GLP-1 agonist**, stands out as an advantageous choice due to its efficacy in promoting weight loss, which is particularly pertinent for obese patients. Liraglutide functions by inhibiting glucagon release and enhancing insulin secretion when nutrients are ingested orally. Furthermore, GLP-1 agonists have received authorisation for use in weight management.

ATP-sensitive potassium channel inhibitors, commonly referred to as sulfonylureas, operate by obstructing the ATP-sensitive potassium channels within pancreatic beta cells. This blockade triggers cell depolarisation and the opening of voltage-dependent calcium channels. The resulting calcium influx initiates insulin release. The patient is currently being treated with gliclazide, which belongs to this class.

DPP-4 inhibitors, or gliptins, exert their effect by blocking the enzyme responsible for degrading GLP-1. This inhibition amplifies the action of endogenous GLP-1 in decreasing glucagon release and augmenting postprandial insulin secretion. Linagliptin is the DPP-4 inhibitor included in the patient's regimen.

PPAR-gamma agonists, also known as thiazolidinediones (e.g., pioglitazone), improve peripheral insulin sensitivity through modulation of genes involved in glucose and lipid metabolism. However, given this patient's obesity, GLP-1 agonists are deemed more suitable.

SGLT-2 inhibitors such as empagliflozin act by facilitating glucose excretion via urine to lower blood glucose levels. Yet again, due to the patient's obesity profile, GLP-1 agonists are considered a more appropriate therapeutic option.

👍 👎 💬 Discuss Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes

- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

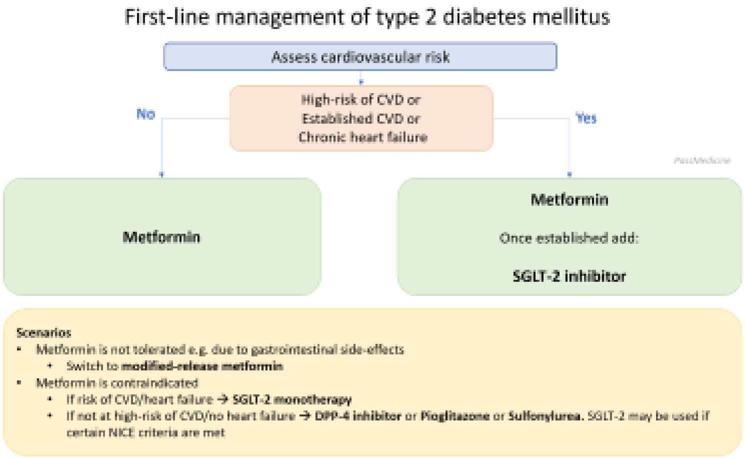
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	**HbA1c target**
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or
Established CVD or
Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios
- Metformin is not tolerated e.g. due to gastrointestinal side-effects
    - Switch to **modified-release metformin**
- Metformin is contraindicated
    - If risk of CVD/heart failure → **SGLT-2 monotherapy**
    - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

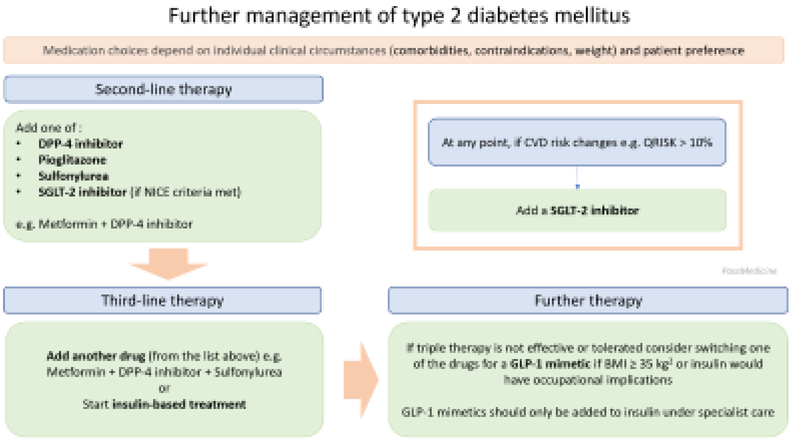
Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.
- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors
- should also be given in addition to metformin if any of the following apply:
    - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
    - the patient has established CVD
    - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated
- if the patient has a risk of CVD, established CVD or chronic heart failure:
    - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
    - DPP-4 inhibitor or pioglitazone or a sulfonylurea
    - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
• DPP-4 inhibitor
• Pioglitazone
• Sulfonylurea
• SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

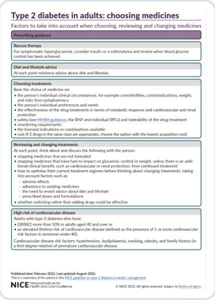
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

Published date: February 2022. Last updated: August 2022.
This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

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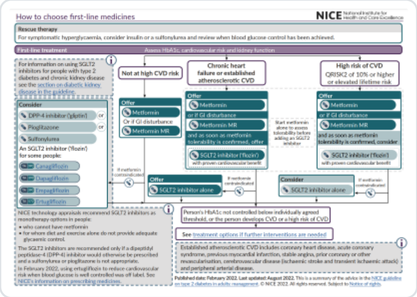

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment — Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider: DPP-4 inhibitor ('gliptin') or Pioglitazone or Sulfonylurea. An SGLT2 inhibitor ('flozin') for some people: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Not at high CVD risk — Offer: Metformin. Or if GI disturbance: Metformin MR

Chronic heart failure or established atherosclerotic CVD — Offer: Metformin, or if GI disturbance Metformin MR, and as soon as metformin tolerability is confirmed, offer SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD, QRISK2 of 10% or higher or elevated lifetime risk — Offer: Metformin, or if GI disturbance Metformin MR, and as soon as metformin tolerability is confirmed, consider SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated — Offer: SGLT2 inhibitor alone

If metformin contraindicated — Consider: SGLT2 inhibitor alone

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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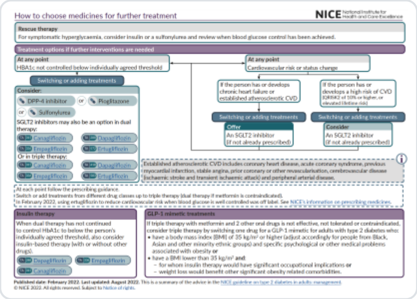

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point HBA1c not controlled below individually agreed threshold

Switching or adding treatments — Consider: DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT2 inhibitors may also be an option in dual therapy: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin. Or in triple therapy: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

At any point Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD — Switching or adding treatments — Offer: An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk) — Switching or adding treatments — Consider: An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs). Dapagliflozin, Empagliflozin, Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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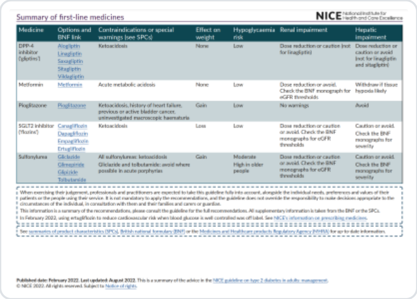

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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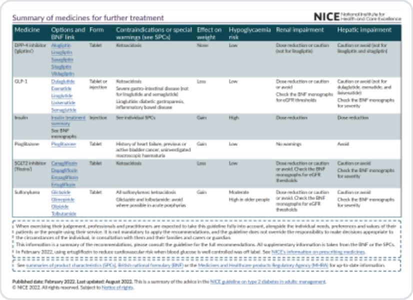

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

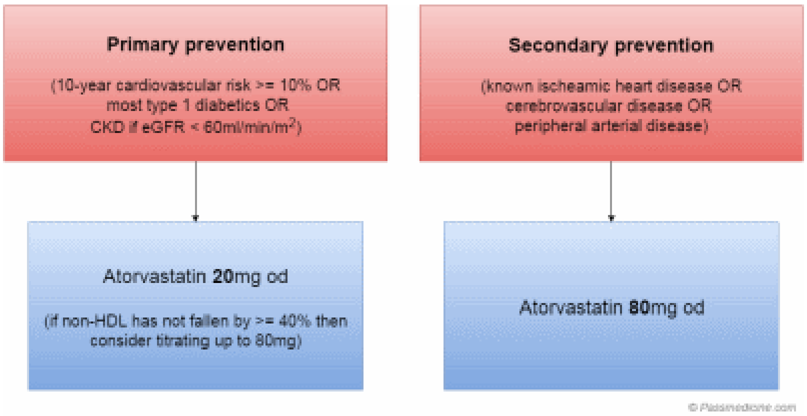
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
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Graphic showing choice of statin.

Next question

Textbooks

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Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

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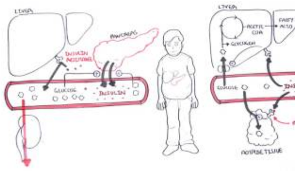
Media

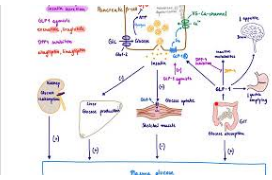


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

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Score: **26.7%**

1 ✓
2 ✓
3 ✓

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Question 87 of 414 ✕

A 32-year-old man is referred to endocrinology from his GP with a three-month history of polyuria and polydipsia. He has a background of bipolar disorder for which he has been taking lithium for six months.

Neurological examination is normal apart from a fine tremor.

His blood test results are as follows:

Na^+	144 mmol/L	(135 - 145)
K^+	4.5 mmol/L	(3.5 - 5.0)
Urea	7.2 mmol/L	(2.0 - 7.0)
Creatinine	100 µmol/L	(55 - 120)
Glucose	6.8 mmol/L	(4.0-7.0)

Following monitored fluid deprivation for eight hours, his urine osmolality is measured as follows:

Urine osmolality	250 mOsm/kg	(50 - 1200)

For the next part of the test, desmopressin is prescribed.

What is the most likely urine osmolality result following administration of desmopressin?

🟩	250 mOsm/kg	67%
	500 mOsm/kg	11%
🟥	750 mOsm/kg	13%
	1000 mOsm/kg	3%
	1250 mOsm/kg	5%

Water deprivation test: nephrogenic DI

- urine osmolality after fluid deprivation: low

- urine osmolality after fluid deprivation: low
- urine osmolality after desmopressin: low

Important for me Less important

The correct answer is 250 mOsm/kg.

This patient is presenting with polyuria and polydipsia with a raised plasma osmolality (can be calculated as 302mOsm/kg).

Normal urine osmolality has a wide range between 50 and 1200 mOsm/kg depending on the state of hydration.

While patients with psychiatric problems are more likely to have psychogenic polydipsia, if this was the diagnosis water deprivation would result in concentrated urine.

A rise in urine osmolality to >700 mOsm/kg is a normal response to dehydration. However, following water deprivation his urine does not concentrate, suggesting diabetes insipidus (DI).

Lithium causes nephrogenic DI. Given that the patient takes lithium and there are no risk factors for cranial DI (e.g. recent surgery, head injury or signs of a pituitary tumour), the most likely cause is nephrogenic DI. We would therefore expect the urine to remain dilute (<300 mOsm/kg) following administration of desmopressin.

All of the other options represent increased concentration of his urine following desmopressin, which would indicate cranial diabetes insipidus.

👍 👎 Discuss (5) Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method

- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

Textbooks

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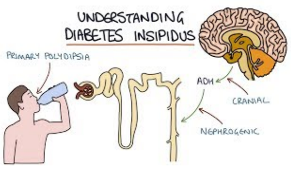
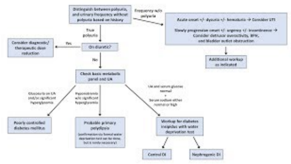
Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5



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Question 88 of 414 ✗

Which one of the following is most likely to be seen in a patient with multiple endocrine neoplasia (MEN) type I?

	Phaeochromocytoma	20%
🟩	Insulinoma	64%
	Marfanoid body habitus	2%
🟥	Medullary thyroid carcinoma	9%
	RET gene	6%

The correct answer is **Insulinoma**. Multiple Endocrine Neoplasia type I (MEN1) is a syndrome characterised by tumours of the parathyroid glands, anterior pituitary, and pancreatic islet cells. An insulinoma is a neuroendocrine tumour derived from the pancreatic beta cells that produce insulin. In MEN1, these types of tumours are quite common. Insulinomas may lead to hypoglycaemia due to excessive insulin production.

The first incorrect option is **Phaeochromocytoma**. While Phaeochromocytomas, which are adrenal gland tumours that secrete catecholamines, can occur in conjunction with endocrine disorders, they are not characteristic of MEN1. Instead, they are more commonly associated with Multiple Endocrine Neoplasia type II (MEN2).

Next we have **Marfanoid body habitus**, which is also an incorrect answer. Marfanoid body habitus refers to physical characteristics similar to those seen in Marfan syndrome such as tall stature, long limbs and fingers, and flexible joints. This feature is not typically associated with MEN1 but rather with conditions like Marfan syndrome or Ehlers-Danlos syndrome.

Medullary thyroid carcinoma is another incorrect option. Medullary thyroid carcinoma arises from parafollicular C cells of the thyroid gland and secretes calcitonin. It's a feature of MEN2 rather than MEN1.

Lastly, the presence of a mutation in the **RET gene** does not fit with MEN1 either. Mutations in this gene are linked to MEN2 and familial medullary thyroid carcinoma but not to MEN1; mutations in the menin gene (MEN1) cause multiple endocrine neoplasia type 1.

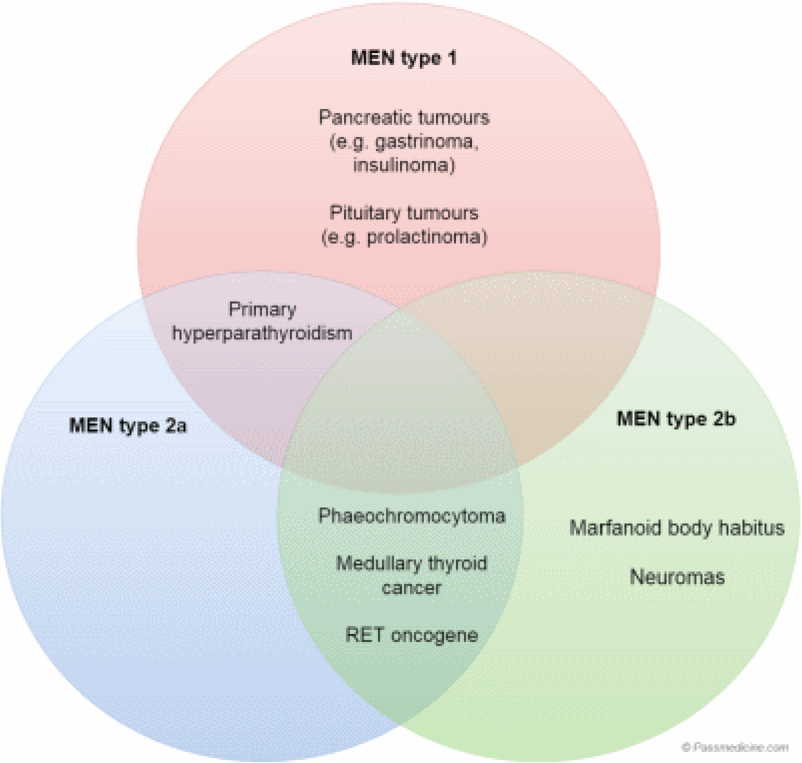
Discuss (3) Improve

Next question

Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	Medullary thyroid cancer 1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
© Passmedicine.com

Venn diagram showing the different types of MEN and their associated features

Next question

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Media

PANCREATIC NEUROENDOCRINE NEOPLASMS

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Question 89 of 414 ✓

A 35-year-old woman is admitted to the hospital due to new-onset headaches associated with vomiting and changes in her vision. On examination, she has bitemporal hemianopia.

An MRI scan of her head identifies a 15mm solid suprasellar mass.

A pituitary blood profile shows the following:

Prolactin:	14 mU/L	(0-15 mU/l)
FSH:	15 IU/L	(25-135 IU/l)
LH:	1.3 IU/L	(2.0-12.0 IU/l)
TSH	3.2 mU/L	(0.35-4.5 mU/l)
Free T4	11.5 pmol/L	(9.0-18.0)
GH post insulin tolerance test:	3.0 /µg/L	(>5.0)
IGF-I	4.2 nmol/L	(6.0-36.0)

ACTH stimulation test shows:

8am Cortisol (baseline)	326 nmol/L	(171-536nmol/l)
Cortisol (30 min after stimulation)	695 nmol/L	(>550 nmol/l)

What condition is the most likely cause of her presentation?

Addison's disease	4%
Cerebral lymphoma	1%
Craniopharyngioma	18%
[✓ Non-functioning pituitary adenoma]	72%
Prolactinoma	5%

Non-functioning pituitary tumours present with hypopituitarism and pressure effects

Non-functioning pituitary tumours present with hypopituitarism and pressure effects

Important for me Less important

The most likely diagnosis is a non-functioning pituitary macroadenoma which presents as a suprasellar mass with pressure effects, such as headaches, visual changes and vomiting and hypopituitarism with non-functioning pituitary tumours. In adults, typically the most common early complaints related to gonadotropin hormone deficiencies such as loss of libido or amenorrhoea in women.

Addison's disease is due to primary adrenal insufficiency with signs and symptoms normal include abdominal, discomfort, gastrointestinal abnormalities, weakness, and weight loss. Hyperpigmentation of the skin can also be noted. As the condition is due to an issue with the adrenal glands the pituitary is not involved and therefore patients do not experience symptoms secondary to optical chiasm compression etc. This patient's presentation is not in keeping with Addison's disease as confirmed by normal levels of cortisol and normal ACTH stimulation tests.

Cerebral lymphoma is a differential diagnosis for a brain lesion however this lesion is more typical in location and signs/symptoms with a pituitary adenoma.

Craniopharyngiomas are tumours that derive from Rathke's pouch, a fetal structure that eventually gives rise to the anterior pituitary gland. It can also cause hypopituitarism and pressure-type effects, but it would more commonly affect children. Additionally, pituitary adenomas constitute 80% of sellar lesions, whereas craniopharyngiomas represent only 1 to 3% of intracranial tumours.

Whilst **prolactinomas** are the most common type of pituitary tumour, this hormone profile shows normal prolactin. This pituitary tumour is **non-functioning** with low levels of growth hormone and sex hormones which are often the first to be affected in terms of hypopituitarism.

Discuss (4) Improve

Next question

Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:

- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)

- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:

- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
  - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:

- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:

- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of

- medical therapy:
  - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
  - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas

  - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery
  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

Textbooks

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Extended textbook

Links

Patient.info 👍 7 👎 0

Pituitary tumours review

Report broken link

Score: **27%**

1 ✓

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Question 90 of 414 ×

A 44-year-old woman presents to her GP complaining of dry eyes. This has been getting worse for the last 3 months. You prescribe some eye lubricant drops, but she comes back a month later complaining of dry mouth and sexual dysfunction.

You send off a series of blood tests, which are shown below.

Hb	140 g/L	Male: (135-180) Female: (115 - 160)
Platelets	255 * 10^9/L	(150 - 400)
WBC	5.0 * 10^9/L	(4.0 - 11.0)
Na^+	136 mmol/L	(135 - 145)
K^+	2.9 mmol/L	(3.5 - 5.0)
Bicarbonate	20 mmol/L	(22 - 29)
Chloride	105 mmol/L	(98 - 107)
pH	7.30	(7.35 - 7.45)
Anti SS-A Antibodies	Positive	

What is the likely cause of the reduced pH in this patient?

	Addison's disease	7%
	Cushing's syndrome	4%
🟩	Type 1 (distal) renal tubular acidosis	61%
🟥	Type 2 (proximal) renal tubular acidosis	21%
	Type 4 renal tubular acidosis	7%

Type 1 (**distal**) renal tubular acidosis may be caused by Sjogren's syndrome

Important for me Less important

This patient has a diagnosis of Sjogren's syndrome, indicated by her dry eyes and mouth and positive anti-SS-A antibodies (also called anti-Ro). We then find an acidosis on her blood tests. Given the low bicarbonate and the history we have, this is likely to be metabolic rather than respiratory.

The next step in investigating metabolic acidosis is to examine the anion gap. As a rule, if you are provided with bicarbonate, chloride, and sodium levels, it is likely to be of use to calculate this gap. The generally agreed formula for this is Na-(Cl+HCO3). In this case, we have 136-(105+20), which equals 11. This is within the normal range (8-16).

Causes of a metabolic acidosis with a normal anion gap include renal tubular acidosis, diarrhoea, hypoaldosteronism, and carbonic anhydrase inhibitors.

Renal tubular acidosis (RTA) type 1 is caused by a failure of the renal cortical collecting duct to secrete hydrogen ions. It presents with a normal anion gap metabolic acidosis, hypokalemia, and hypercalciuria. It is also associated with Sjogren's syndrome, making it the most likely cause in this case.

Addison's disease can present with metabolic acidosis with a normal anion gap. However, it also causes hyperkalaemia, hypotension, and hyponatraemia, and is not associated with Sjogren's syndrome. This is therefore incorrect in this case.

Cushing's syndrome, on the other presents with hypokalaemia, hypernatraemia, hypertension, and a metabolic alkalosis. It is therefore not correct in this case.

RTA type 2 is caused by a failure of the proximal tubular cells to reabsorb bicarbonate. It presents similarly to RTA 1, with hyponatraemia and a normal anion gap metabolic acidosis. However, it is not associated with Sjogren's syndrome, making it less likely in this case.

RTA type 4 is not a tubular pathology per se, but is rather secondary to hypoaldosteronism. This results in reduced proximal tubular ammonium excretion. It results in a hyperkalaemic metabolic acidosis, and so is not the cause in this case.

👍 👎 Discuss (4) Improve

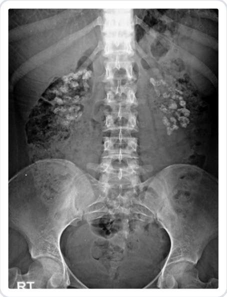
Next question

Renal tubular acidosis ★

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

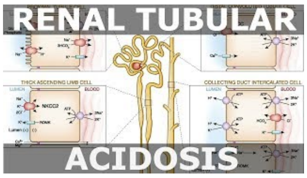
Next question

Textbooks

High-yield textbook

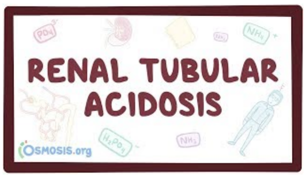
Extended textbook

Media


RENAL TUBULAR
ACIDOSIS

Renal tubular acidosis

DirtyUSMLE - YouTube 👍 177 👎 4


RENAL TUBULAR
ACIDOSIS
OSMOSIS.org

Renal tubular acidosis

Osmosis - YouTube 👍 39 👎 3

Report broken media

Score: **26.7%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

PassMedicine

← Question 91 of 414 ✗ ⚐ →

You review a 52-year-old man who is being investigated for weight gain, impotence and hypertension. On examination you record a blood pressure of 180/110 mmHg and notice purple striae around his abdomen. He also has some difficulty getting up from a chair and you observe generalised decreased muscle strength. Routine bloods are ordered. Given the likely underlying diagnosis, what are the urea and electrolytes most likely to show?

	Hypokalaemic metabolic acidosis	15%
	Hyperkalaemic metabolic alkalosis	7%
🟥	Hypocalcaemic metabolic acidosis	2%
🟩	Hypokalaemic metabolic alkalosis	69%
	Hyperkalaemic metabolic acidosis	6%

Cushing's syndrome - hypokalaemic metabolic alkalosis

Important for me Less important

The correct answer is **Hypokalaemic metabolic alkalosis**. This patient's presentation of weight gain, impotence, hypertension, purple striae, and decreased muscle strength is suggestive of Cushing's syndrome. Cushing's syndrome can be caused by an excess of cortisol production from the adrenal glands or exogenous glucocorticoid use. The excess cortisol can lead to sodium and water retention, causing hypertension and hypokalaemic metabolic alkalosis. In this case, the urea and electrolytes would most likely show low potassium levels with a concurrent metabolic alkalosis.

Hypokalaemic metabolic acidosis is not the most likely finding in this scenario. While hypokalaemia might be present due to increased mineralocorticoid activity from cortisol, metabolic acidosis would not be expected in Cushing's syndrome.

Hyperkalaemic metabolic alkalosis is also unlikely in this case. Hyperkalaemia is not typically associated with Cushing's syndrome as cortisol has mineralocorticoid activity that leads to increased potassium excretion and subsequent hypokalaemia. Additionally, although there may be a component of metabolic alkalosis due to the mineralocorticoid effects of cortisol, it would not coexist with hyperkalaemia.

Hypocalcaemic metabolic acidosis does not fit the clinical picture presented for this patient. Hypocalcaemia may result from various causes such as chronic kidney disease or primary hypoparathyroidism; however, these conditions do not align with the symptoms described for this patient (weight gain, impotence, hypertension). Furthermore, while hypocalcaemia could potentially cause muscle weakness or tetany-like symptoms in severe cases, it would not explain the other features observed in this patient.

Finally, **Hyperkalaemic metabolic acidosis** is also implausible given the patient's presentation. As mentioned earlier, Cushing's syndrome is more likely to cause hypokalaemia due to the mineralocorticoid effects of cortisol. Additionally, metabolic acidosis would not be expected in this case, as the excess cortisol would typically lead to a metabolic alkalosis instead.

Discuss (3) Improve

Next question

Cushing's syndrome: investigations

This section will consider:

- the general lab findings consistent with Cushing's syndrome
- tests to confirm whether a patient indeed has Cushing's syndrome
- tests to find the underlying cause of Cushing's syndrome

It is useful to bear in mind the possible causes:

- iatrogenic: corticosteroid therapy
- ACTH-dependent causes
  - Cushing's disease (a pituitary adenoma → ACTH secretion)
  - ectopic ACTH secretion secondary to a malignancy
- ACTH-independent causes
  - adrenal adenoma

General findings consistent with Cushing's syndrome

A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance.

Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels.

Tests to confirm Cushing's syndrome

The three most commonly used tests are:

- overnight (low-dose) dexamethasone suppression test
    - this is the most sensitive test and is now used first-line to test for Cushing's syndrome
    - patients with Cushing's syndrome do not have their morning cortisol spike suppressed
- 24 hr urinary free cortisol
    - two measurements are required
- bedtime salivary cortisol
    - two measurements are required

Localisation tests

The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

High-dose dexamethasone suppression test

The high-dose dexamethasone suppression test may be used to localise the pathology resulting in Cushing's syndrome. This test may be interpreted as follows:

Cortisol	**ACTH**	**Interpretation**
Not suppressed	Suppressed	Cushing's syndrome due to other causes (e.g. adrenal adenomas)
Suppressed	Suppressed	Cushing's disease (i.e. pituitary adenoma → ACTH secretion)
Not suppressed	Not suppressed	Ectopic ACTH syndrome

Other tests

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic ACTH secretion.

An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's.

Next question

Textbooks

High-yield textbook

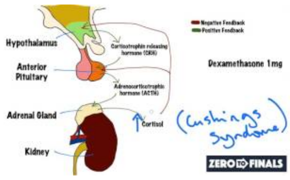
Extended textbook

Media

CUSHING SYNDROME

Cushing syndrome

Osmosis - YouTube 👍 35 👎 2


Negative Feedback
Positive Feedback
Hypothalamus
Corticotrophin releasing hormone (CRH)
Anterior Pituitary
Dexamethasone 1mg
Adrenocorticotrophic hormone (ACTH)
Adrenal Gland
Cortisol
(Cushings Syndrome)
Kidney
ZERO TO FINALS

Understanding The Dexamethasone Suppression Test

Zero to Finals - YouTube 👍 118 👎 8

Report broken media

PassMedicine

← Question 92 of 414 ✗ ⚐ →

A 65-year-old male attends the clinic with a 3-month history of lethargy and polyuria. He has a past medical history of biventricular heart failure. He takes no regular medications.

Blood results are as follows:

HbA1c	58 mmol/mol	(<42)

The patient is started on metformin which is titrated to the maximal dose.

Repeat blood testing 4 weeks later is as follows:

HbA1c	52 mmol/mol	(<42)

What further treatment is indicated?

🟩	Empagliflozin	67%
🟥	Gliclazide	9%
	Liraglutide	2%
	No further treatment	19%
	Pioglitazone	2%

SGLT-2 inhibitors should be used in addition to metformin as initial therapy for T2DM if CVD, high-risk of CVD or chronic heart failure

Important for me Less important

Empagliflozin is correct. Empagliflozin is a type of SGLT-2 inhibitor. These agents should be used in addition to metformin as initial therapy for T2DM if the patient has cardiovascular disease (CVD), a high-risk of CVD, or chronic heart failure. The patient in this clinical case has established heart failure and should therefore be started on an SGLT-2 inhibitor.

Gliclazide, **Liraglutide**, and **Pioglitazone** are incorrect. These are second-line agents which should be used if the HbA1c has risen to 58 mmol/mol (7.5%) despite the initial measures. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

No further treatment is incorrect. The patient has established heart failure and thus requires the addition of an SGLT-2 inhibitor.

Discuss (4) | Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015
- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly

- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

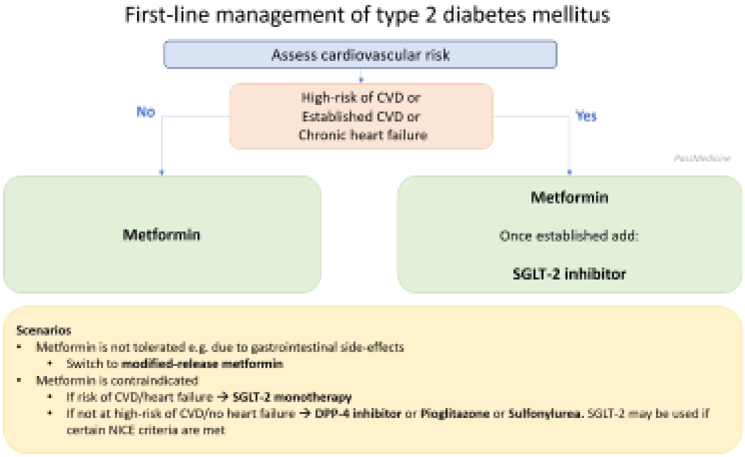
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	**HbA1c target**
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or
Established CVD or
Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios

- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

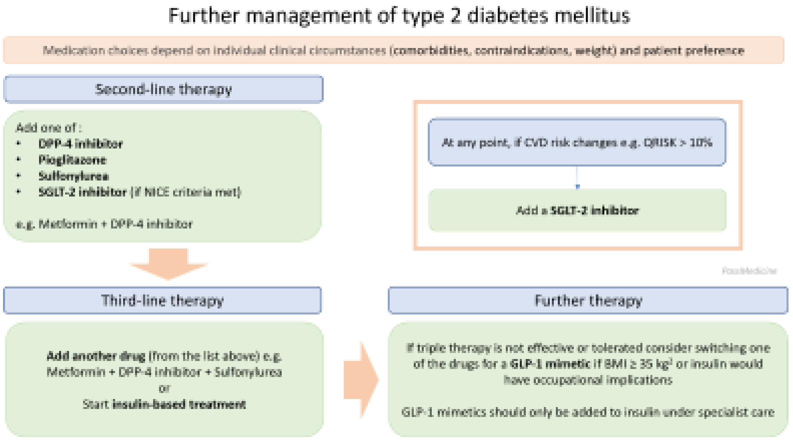
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

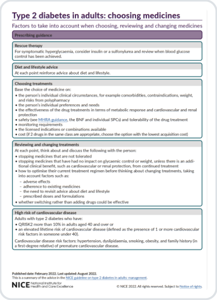
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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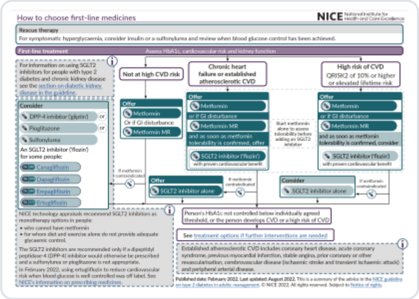

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk

Offer
Metformin
Or if GI disturbance
Metformin MR

If metformin contraindicated

Chronic heart failure or established atherosclerotic CVD

Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

If metformin contraindicated

Offer
SGLT2 inhibitor alone

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk

Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated

Consider
SGLT2 inhibitor alone

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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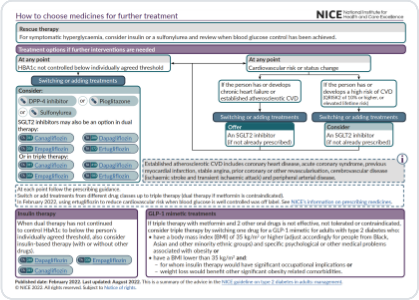

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin
Or in triple therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD

Switching or adding treatments

Offer
An SGLT2 inhibitor
(if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)

Switching or adding treatments

Consider
An SGLT2 inhibitor
(if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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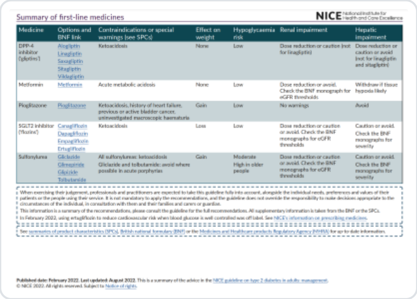

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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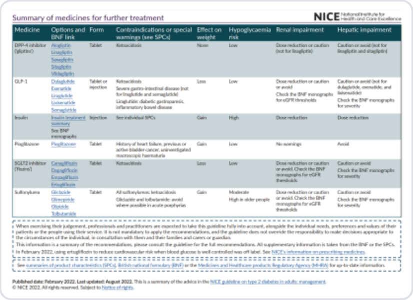

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

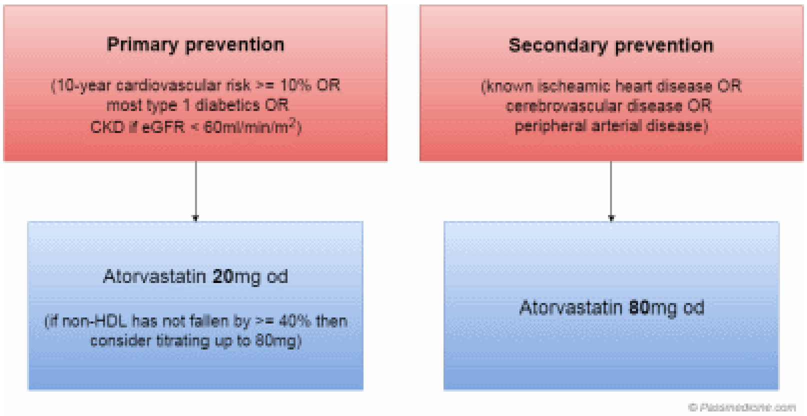
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

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Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

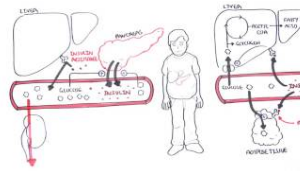
NICE

2022 Type 2 diabetes guidelines

👍 8 👎 5

Report broken link

Media

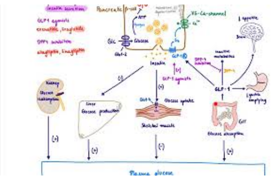


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

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Score: **26.1%**

1 ✓
2 ✓
3 ✓

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Question 93 of 414 ✗

A 40-year-old woman with rheumatoid arthritis is diagnosed as having type 1 renal tubular acidosis. Which one of the following features is most likely to be seen as a consequence?

	Hyperkalaemia	8%
	Osteomalacia	3%
	Decreased bicarbonate reabsorption in the proximal tubule	12%
🟥	Raised anion gap metabolic acidosis	9%
🟩	Nephrocalcinosis	68%

Hypokalaemia, nephrocalcinosis - type 1 renal tubular acidosis

Important for me Less important

Osteomalacia is more commonly seen in type 2 renal tubular acidosis.

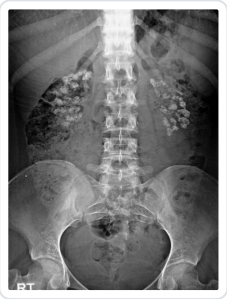
Discuss (1) Improve

Next question

Renal tubular acidosis ★

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)
- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

Textbooks

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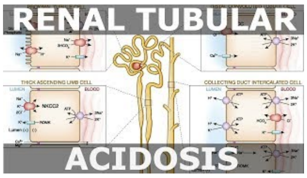
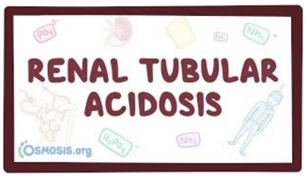

RENAL TUBULAR
ACIDOSIS

Renal tubular acidosis

DirtyUSMLE - YouTube 👍 177 👎 4


RENAL TUBULAR
ACIDOSIS
OSMOSIS.org

Renal tubular acidosis

Osmosis - YouTube 👍 39 👎 3

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Score: **25.8%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗

PassMedicine

Question 94 of 414 ✗

A 42-year-old man presents to the emergency department complaining of long-standing muscle weakness and headaches. His blood pressure is 176/78 mmHg, but all other observations are within normal limits. Examination is unremarkable.

Blood results are as follows:

Na^+	145 mmol/L	(135 - 145)
K^+	2.8 mmol/L	(3.5 - 5.0)
Bicarbonate	34 mmol/L	(22 - 29)
Urea	4 mmol/L	(2.0 - 7.0)
Creatinine	72 µmol/L	(55 - 120)

What is the most appropriate first-line investigation?

	Adrenal vein sampling	1%
🟥	CT abdomen	3%
	Dexamethasone suppression test	17%
🟩	Plasma aldosterone/renin ratio	67%
	Short synacthen test	11%

A plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism

Important for me Less important

Features of hypokalaemia coupled with hypertension are suggestive of primary hyperaldosteronism. This can be caused by an adrenal adenoma (Conn's syndrome) or bilateral idiopathic adrenal hyperplasia. The first line investigation for this is a plasma aldosterone/renin ratio, which should show high aldosterone levels alongside low renin levels.

Adrenal vein sampling and CT abdomen can be useful in differentiating between the different causes of primary hyperaldosteronism, but would not be appropriate first-line investigations.

The short synacthen test is the first-line investigation for adrenal insufficiency. This would typically present with hyponatraemia and hypotension.

Dexamethasone suppression tests are useful in the investigation adrenal gland function and is typically used to investigate for Cushing's disease.

👍 👎 💬 Discuss (6) Improve

Next question

Primary hyperaldosteronism

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes
- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

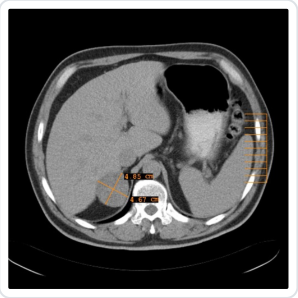
Features
- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations
- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension

- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
    - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
    - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



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Links

The Endocrine Society 👍 5 👎 3

2016: The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment

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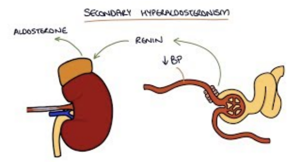
Media


SECONDARY HYPERALDOSTERONISM
ALDOSTERONE
RENIN
↓BP

Hyperaldosteronism and Conn's Syndrome

Zero To Finals - YouTube 👍 47 👎 5

HYPERALDOSTERONISM

Hyperaldosteronism - causes, symptoms, diagnosis, treatment, pathology

Osmosis - YouTube 👍 43 👎 6

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Score: **25.5%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗
12 ✓

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Question 95 of 414 ✗

A 32-year-old male presents with a 10-day history of a worsening rash on his back and chin. He does not complain of pain or pruritus but is concerned as the rash is unsightly. His past medical history includes ulcerative colitis which is being treated with prednisolone due to a recent flare-up 7 weeks ago and is responding well. He does not smoke, use tobacco nor alcohol and works as a gardener.

On examination, he has uniform papules with some small pustules with moderate erythema over his upper trunk, back and jaw. There are no comedones nor cysts. Vital signs are normal.

Which of the following is the most likely cause of this patient's skin rash?

	Acne vulgaris	15%
🟩	Drug-induced adverse effect	48%
	Erythema nodosum	14%
	Occupational exposure to herbicides	4%
🟥	Suppurative folliculitis (*Pseudomonas aeruginosa*)	18%

Systemic glucocorticoids can cause drug-induced acne. This is characterised as monomorphic papular rash without comedones or cysts. This does not respond to acne treatment but improves on drug discontinuation

Important for me Less important

This patient has drug-induced acne is most commonly caused by glucocorticoids and androgens but can also be precipitated by azathioprine, phenytoin, antipsychotics, and isoniazid [1]

This typically presents as monomorphic papules and pustules with no comedones, cysts or nodules within 2 weeks of starting medication. This subset of patients will not respond to standard acne treatment, discontinuation of offending agents typically clears up the rash.

Acne vulgaris displays lesions in **various stages of development** and typically occurs in the face in adolescence.

Dermal manifestations of IBD include erythema nodosum, pyoderma and pyoderma gangrenosum. Erythema nodosum presents as tender red nodules, typically on legs and arms.

Herbicides, fungicides, and insecticides contain halogenated aromatic hydrocarbons. Halogenated compounds can cause occupational acne (also known as chloracne). This rash is characterised by inflammatory nodules and large comedones.

Suppurative folliculitis is most often caused by *Staphylococcus aureus* , it can also be caused by pseudomonas.

References
(1) 4. Du-Thanh A, Kluger N, Bensalleh H, Guillot B. Drug-Induced Acneiform Eruption. American Journal of Clinical Dermatology. 2011;12(4):233-245.

👍 👎 Discuss (2) Improve

Next question

Corticosteroids: side-effects ★

Glucocorticoid side-effects

- endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, hyperlipidaemia
- Cushing's syndrome: moon face, buffalo hump, striae
- musculoskeletal: osteoporosis, proximal myopathy, avascular necrosis of the femoral head
- immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis
- psychiatric: insomnia, mania, depression, psychosis
- gastrointestinal: peptic ulceration, acute pancreatitis
- ophthalmic: glaucoma, cataracts
- dermatological: acne
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Next question

PassMedicine

Question 96 of 414

Which one of the following may be associated with galactorrhoea?

Primary hypothyroidism	38%
Addison's disease	5%
Cushing's syndrome	15%
Grave's disease	6%
Bromocriptine	36%

The correct answer is **Primary hypothyroidism**. Galactorrhoea, the spontaneous flow of milk from the breast unrelated to childbirth or nursing, can be associated with primary hypothyroidism. Hypothyroidism can lead to an increase in thyrotropin-releasing hormone (TRH) which stimulates prolactin release leading to galactorrhoea. Primary hypothyroidism is also associated with hyperprolactinaemia, which can cause galactorrhoea.

Addison's disease, although an endocrine disorder like primary hypothyroidism, does not typically cause galactorrhoea. Addison's disease primarily affects the adrenal glands and results in a deficiency of hormones such as cortisol and aldosterone. It has no direct effect on prolactin levels or lactation.

Cushing's syndrome is characterised by excess cortisol production and does not usually result in galactorrhoea. While Cushing's syndrome can have wide-ranging effects on the body due to high levels of cortisol, it does not directly stimulate prolactin production or lactation.

Grave's disease is a form of hyperthyroidism and is not typically associated with galactorrhoea. Grave's disease results in an overproduction of thyroid hormones but does not directly affect prolactin levels or lactation.

Finally, **Bromocriptine** is actually used as a treatment for conditions that cause galactorrhoea such as hyperprolactinaemia. Bromocriptine works by inhibiting prolactin secretion thus it would reduce rather than cause galactorrhoea.

Discuss (4) Improve

Next question

Prolactin and galactorrhoea

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. Dopamine acts as the primary prolactin releasing inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- prolactinoma
- pregnancy
- oestrogens
- physiological: stress, exercise, sleep
- acromegaly: 1/3 of patients
- polycystic ovarian syndrome
- primary hypothyroidism (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- metoclopramide, domperidone
- phenothiazines
- haloperidol
- very rare: SSRIs, opioids

Next question

Textbooks

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Links

Patient.info 👍 2 👎 1

Galactorrhoea review

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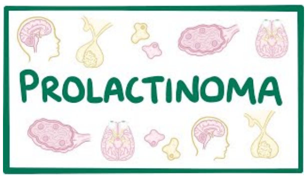
Media



Prolactinoma

Osmosis - YouTube 👍 15 👎 1

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Score: **25%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

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Question 97 of 414 ✓

An insulin stress test is most useful in the investigation of:

Glucagonoma	27%
Insulinoma	31%
Addison's disease	9%
Hypopituitarism	31%
Diabetes mellitus	2%

The correct answer is **Hypopituitarism**. An insulin stress test (IST) is primarily used to assess the integrity of the hypothalamic-pituitary-adrenal axis, and it is considered the gold standard for diagnosing hypopituitarism. In this test, insulin-induced hypoglycaemia should stimulate the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal glands to produce cortisol. If there's a deficiency in ACTH due to hypopituitarism, cortisol response will be inadequate.

Glucagonoma is incorrect because this rare pancreatic tumour secretes glucagon excessively, leading to hyperglycaemia. The diagnosis of glucagonoma typically involves measuring serum glucagon levels and imaging studies rather than an insulin stress test.

Insulinoma, while related to insulin, isn't best diagnosed with an IST either. An insulinoma is a tumour of the pancreas that overproduces insulin, causing hypoglycaemia. Diagnosing an insulinoma usually involves demonstrating inappropriate secretion of insulin despite low blood glucose levels and localising the tumour using imaging techniques.

Addison's disease or primary adrenal insufficiency can also be ruled out as the correct answer. While an IST can indicate adrenal insufficiency if cortisol response is poor, Addison's disease specifically refers to primary failure of the adrenal glands rather than pituitary dysfunction (which would be indicated by an IST). Therefore, other tests such as measuring morning cortisol levels or performing a short Synacthen test are more commonly used first-line investigations.

Finally, **Diabetes mellitus** also doesn't fit as diabetes is characterised by high blood sugar levels due to insufficient production or use of insulin by the body. It's typically diagnosed through direct measurement of blood glucose levels under fasting conditions or through a glucose tolerance test rather than an IST.

Discuss (6) Improve

Next question

Insulin stress test ★

Basics

- used in investigation of hypopituitarism
- IV insulin given, GH and cortisol levels measured
- with normal pituitary function GH and cortisol should rise

Contraindications

- epilepsy
- ischaemic heart disease
- adrenal insufficiency

Next question

Textbooks

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Question 98 of 414 ✗

A 32-year-old woman is 24 weeks pregnant. This is her first pregnancy. She has no significant past medical history and is on no regular medications. She does not smoke or drink alcohol.

On examination, the symphysis-fundal height is consistent with the estimated gestation. She has a raised body mass index (32 kg/m²).

An oral glucose tolerance test is arranged.

Fasting blood glucose	6.2 mmol/L	(<5.1)
Glucose level (2h)	7.9 mmol/L	(<6.4)

She is given diet and lifestyle advice and reviewed in clinic two weeks later with repeat fasting blood glucose level.

Fasting blood glucose	5.9 mmol/L	(<5.1)

Metformin is commenced and she is reviewed one week later where her fasting glucose is repeated.

Fasting blood glucose	5.8 mmol/L	(<5.1)

What is the appropriate management at this point?

	Commence gliclazide	2%
🟩	Commence insulin	82%
🟥	Commence linagliptin	2%
	Commence liraglutide	0%
	Continue metformin	13%

In gestational diabetes, if blood glucose targets are not met with diet/metformin then insulin should be added

Important for me Less important

Commence insulin is the correct answer. If a pregnant woman fails to meet blood glucose targets (fasting blood sugar < 5.3 mmol/L) despite a trial of diet and metformin, insulin should be commenced.

Commence gliclazide is incorrect. The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

Commence linagliptin is incorrect. The BNF advises linagliptin should be avoided in pregnancy due to lack of data. It has no place in the current guidelines for the management of hyperglycaemia in pregnancy.

Commence liraglutide is incorrect. Toxicity in pregnancy was noted in animal studies.

Continue metformin is incorrect. This woman has not met targets levels for fasting blood glucose levels with a trial of diet and metformin and therefore needs additional therapy. Insulin is most appropriate.

👍 👎 Discuss (7) Improve

Next question

Gestational diabetes ★

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:

- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes

- BMI of > 30 kg/m^2
- previous macrosomic baby weighing 4.5 kg or above

- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates

- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

NICE 👍 3 👎 5

2015 Management of diabetes in pregnancy

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← Question 99 of 414 ✗ →

A 24-year-old woman is brought to the emergency department by ambulance with a reduced level of consciousness. She has a past medical history of type 1 diabetes mellitus and borderline personality disorder. She is on regular insulin.

On examination, her Glasgow coma scale is 3/15.

Venous blood gas:

pH	7.36	(7.35-7,45)
K+	3.8 mmol/L	(3.5-4.5)
Na+	136 mmol/L	(135-145)
Glucose	1.2 mmol/L	(4.0-7.0)
HCO3-	23 mmol/L	(22-26)
Hb	145 g/dL	(12.1 - 15.1)

Given the likely diagnosis, which hormone is first to be secreted in response?

🟥	Cortisol	15%
🟩	Glucagon	76%
	Growth hormone	2%
	Insulin	3%
	Glucagon-like peptide-1	4%

Glucagon is the first hormone secreted in response to hypoglycaemia

Important for me Less important

Glucagon is the correct answer. The patient's reduced level of consciousness is explained by profound hypoglycaemia, likely as a consequence of exogenous insulin administration. Patients with borderline personality disorder have a higher incidence of self harm and suicidality than the general population. Glucagon is a counter-regularly hormone that seeks to raise the blood glucose level and is the first hormone to be secreted in response to hypoglycaemia.

Insulin is incorrect. Insulin secretion decreases in response to hypoglycaemia. Additionally, this patient will have an absolute deficiency as she has T1DM.

Cortisol is incorrect. This is another counter-regularly hormone that will be secreted in an attempt to raise the blood glucose level in response to hypoglycaemia. However, this hormone takes longer to be secreted.

Glucagon-like peptide-1 is incorrect. This hormone causes glucose-dependent insulin secretion and therefore would not be secreted in response to hypoglycaemia.

Growth hormone is incorrect. This is another counter-regularly hormone that will be secreted in an attempt to raise the blood glucose level in response to hypoglycaemia. However, this hormone takes longer to be secreted.

Discuss (4) Improve

Next question

Hypoglycaemia

Causes
- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
    - causes exaggerated insulin secretion
    - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia
- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous

system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
  - Sweating
  - Shaking
  - Hunger
  - Anxiety
  - Nausea
- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
  - Weakness
  - Vision changes
  - Confusion
  - Dizziness
- Severe and uncommon features of hypoglycaemia include:
  - Convulsion
  - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):
  - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
  - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
  - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
  - If the patient is alert, a quick-acting carbohydrate may be given (as above)
  - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
  - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

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Question 100 of 414 ✗

A 41-year-old man with known type 2 diabetes presents with severe central chest pain. An NSTEMI is diagnosed based on ECG changes and an increased troponin level. Angiography performed a few days later confirms the presence of coronary artery disease.

The patient is already established on metformin 1g twice daily. Hb1Ac is measured at 48mmol/mol (6.5%). Three months ago, their HbA1c was 50 mmol/mol (6.7%).

How should this patient's diabetes be managed?

No changes required	28%
Start an DPP-4 inhibitor	5%
🟩 Start an SGLT-2 inhibitor	61%
Start pioglitazone	2%
🟥 Titrate up metformin	4%

In patients with T2DM, SGLT-2 should be introduced at any point they develop CVD, a high risk of CVD or chronic heart failure

Important for me Less important

This patient has established type 2 diabetes and, although they are well controlled, they have now developed cardiovascular disease (CVD) and are at risk of heart failure. Despite glucose control, **an SGLT-2 inhibitor** should be recommended to patients with type 2 diabetes if they develop CVD or develop a high risk for CVD or chronic heart failure at any point.

Although this patient's glucose levels are well controlled, they have now developed cardiovascular disease, and should therefore be started on an SGLT-2 inhibitor. Making **no change** to their treatment is not suggested.

A **DPP-4 inhibitor** may be considered as an alternative to an SGLT-2 inhibitor however they are not commonly recommended in patients at risk of heart failure as studies have shown they can accelerate/increase the risk of developing the condition. When used, patients must be closely monitored for signs of heart failure.

Pioglitazone is another alternative to SGLT-2 inhibitors however it can also cause fluid retention and can precipitate congestive heart failure. It should be avoided in patients at risk of heart failure such as those with CVD.

This patient is already at the maximum dose of metformin and **titration up of their metformin** is therefore not an option.

👍 👎 Discuss (2) Improve

Next question

Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015
- individual targets should be agreed with patients to encourage motivation

- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

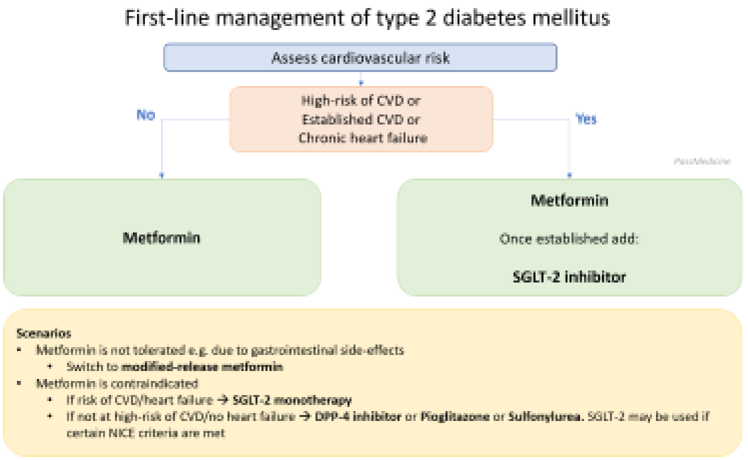
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	**HbA1c target**
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios
- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

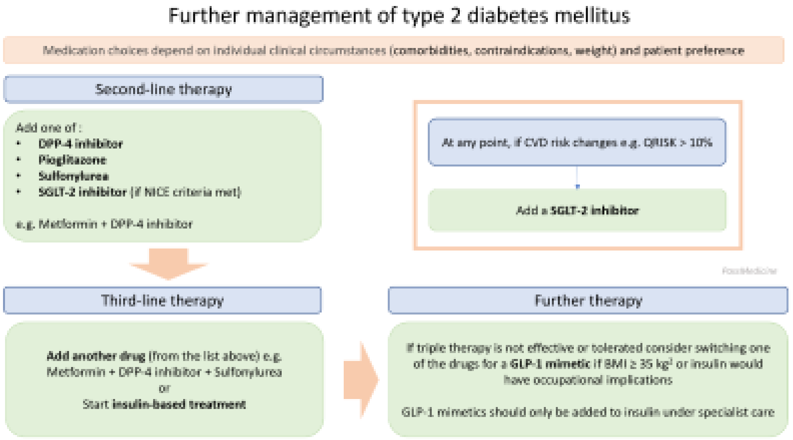
Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.
- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated
- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
• DPP-4 inhibitor
• Pioglitazone
• Sulfonylurea
• SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

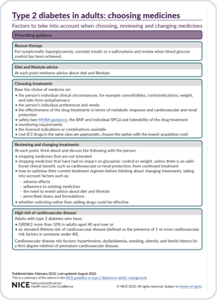
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice
At each point reinforce advice about diet and lifestyle.

Choosing treatments
Base the choice of medicine on:
- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments
At each point, think about and discuss the following with the person:
- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease
Adults with type 2 diabetes who have:
- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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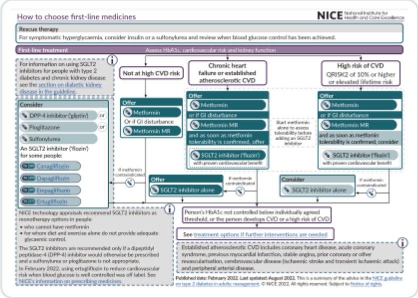

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR

Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated
Offer
SGLT2 inhibitor alone
If metformin contraindicated
Consider
SGLT2 inhibitor alone
If metformin contraindicated

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:
- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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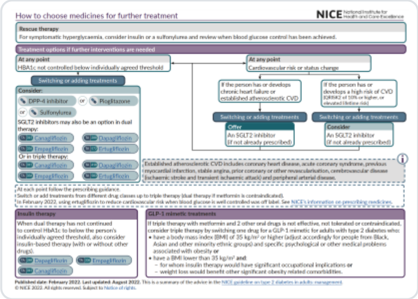

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments
Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin
Or in triple therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy
When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin Empagliflozin
Canagliflozin

GLP-1 mimetic treatments
If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:
- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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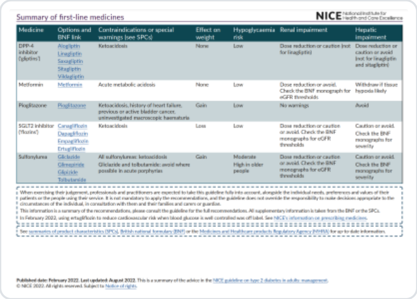

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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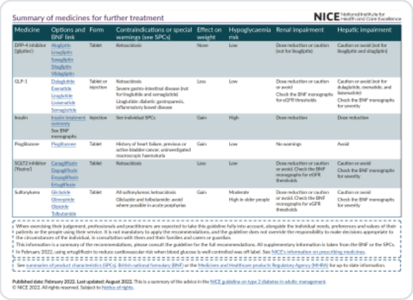

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

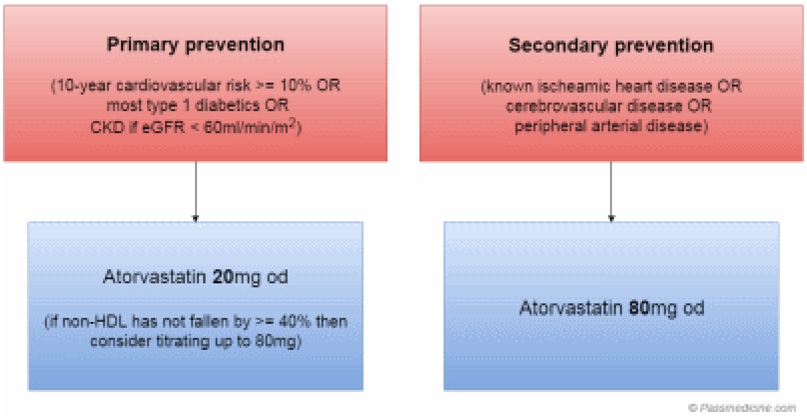
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

PassMedicine

Question 101 of 414 ✗

A 34-year-old woman presents with palpitations, tremor and heat intolerance. She is diagnosed with Graves' disease and started on carbimazole. What is the mechanism of action of this drug?

Inhibits 5'-deiodinase reducing production of T3	13%
Increases renal excretion of carbimazole	0%
Blocks uptake of iodine to thyroid gland by reducing levels of hydrogen peroxide	9%
🟩 Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin	75%
🟥 Increases rate of thyroxine breakdown by thyroid peroxidase	3%

Carbimazole blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production

Important for me Less important

The correct answer to this question is that carbimazole **blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin**. Carbimazole is an antithyroid medication commonly used in the management of hyperthyroidism, such as in Graves' disease. It works by inhibiting the enzyme thyroid peroxidase, which plays a crucial role in the synthesis of thyroid hormones. Thyroid peroxidase catalyses two key reactions: the oxidation of iodide ions to form iodine atoms (which are required for the iodination of tyrosine residues on thyroglobulin) and the subsequent coupling of these iodinated tyrosines to form T3 and T4. By blocking this enzyme, carbimazole reduces thyroid hormone production.

The first option, that carbimazole **inhibits 5'-deiodinase reducing production of T3**, is incorrect. 5'-deiodinase is an enzyme that converts inactive thyroxine (T4) into active triiodothyronine (T3) in peripheral tissues. While inhibition of this enzyme would reduce levels of T3, this is not how carbimazole operates.

Next, **increases renal excretion of carbimazole** is not accurate either. The renal excretion aspect pertains to how the drug is eliminated from the body rather than its mechanism of action in treating hyperthyroidism.

The third incorrect option suggests that carbimazole **blocks uptake of iodine to thyroid gland by reducing levels of hydrogen peroxide**. This statement confuses several aspects related to thyroid hormone synthesis. While it's true that hydrogen peroxide is involved in oxidising iodide ions to form iodine atoms (a step necessary for hormone synthesis), it's not accurate to say that carbimazole functions by reducing levels of hydrogen peroxide or blocking iodine uptake.

Finally, **increases rate of thyroxine breakdown by thyroid peroxidase** isn't correct as well. Thyroid peroxidase isn't involved in breaking down thyroxine; instead, it aids in synthesising T3 and T4. Additionally, increasing the rate at which thyroxine breaks down wouldn't be beneficial for managing hyperthyroidism since more active T3 would be produced.

👍 👎 Discuss (4) Improve

Next question

Carbimazole

Carbimazole is used in the management of thyrotoxicosis. It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.

Mechanism of action
- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production
- in contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5'-deiodinase which reduces peripheral conversion of T4 to T3

Adverse effects
- agranulocytosis
- crosses the placenta, but may be used in low doses during pregnancy

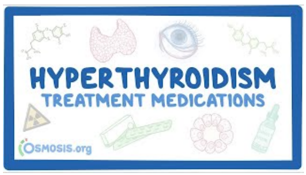
Next question

Textbooks

High-yield textbook

Extended textbook

Media


HYPERTHYROIDISM
TREATMENT MEDICATIONS
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Hyperthyroidism treatment medications

Osmosis - YouTube 👍 13 👎 3

Report broken media

Score: **24.8%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗

PassMedicine

Question 102 of 414 ✓

A 45-year-old woman is brought to the emergency department with fevers and vomiting.

She has a past medical history of adrenal insufficiency, hypertension, hyperthyroidism, and well-controlled schizophrenia on risperidone. She also recently underwent a total abdominal hysterectomy for fibroids.

On examination, she is sweaty, confused, and agitated. Her heart rate is 110 bpm and her blood pressure is 166/113mmHg. Neurological examination is normal.

Bloods are awaited.

What is the most appropriate management?

IV hydrocortisone and fludrocortisone	16%
IV hydrocortisone, propranolol, Lugol's iodine and carbimazole	72%
IV labetalol	3%
IV liothyronine	1%
Stop risperidone, give IV benzodiazepines and dantrolene	8%

Thyrotoxic storm is treated with beta blockers, propylthiouracil and hydrocortisone

Important for me Less important

IV hydrocortisone, propranolol, Lugol's iodine and carbimazole is correct. This patient is likely suffering from a thyrotoxic crisis, evidenced by the precipitant (recent major surgery) and the constellation of confusion, agitation, fever, hypertension, and tachycardia. Treatment is initiated before the thyroid function tests are back. Treatment consists broadly of counteracting the peripheral effects of thyroid hormone (using propranolol), preventing peripheral conversion of T4 to active T3 (using steroids), and inhibiting further thyroid hormone synthesis (using antithyroid drugs and Lugol's iodine).

IV hydrocortisone and fludrocortisone is incorrect. This is the treatment for acute adrenocortical insufficiency, but in the acute phase, only IV hydrocortisone needs to be given. This diagnosis is less likely; acute adrenocortical insufficiency would present with shock and low blood pressure, rather than the hypertension and fever seen in this question.

IV labetalol is incorrect. This would be an appropriate treatment for a hypertensive emergency such as hypertensive encephalopathy. The blood pressure in this case is raised, but not to the point that hypertensive encephalopathy would be a concern. In patients with a diastolic blood pressure over 125mmHg, this should become a consideration.

IV liothyronine is incorrect. This would be the treatment for myxoedema coma; the extreme form of hypothyroidism. This patient, however, is exhibiting signs of *hyper*thyroidism.

Stop risperidone, give IV benzodiazepines and dantrolene is incorrect. This is the treatment for neuroleptic malignant syndrome. Neuroleptic malignant syndrome is characterised by fever, altered GCS, autonomic lability, hypermetabolism, and generalised rigidity. The absence of rigidity makes this diagnosis less likely.

👍 👎 Discuss (2) Improve

Next question

Thyroid storm ★

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating events:
- thyroid or non-thyroidal surgery
- trauma
- infection
- acute iodine load e.g. CT contrast media

Clinical features include:
- fever > 38.5ºC
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test - jaundice may be seen clinically

Management:

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- beta-blockers: typically IV propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

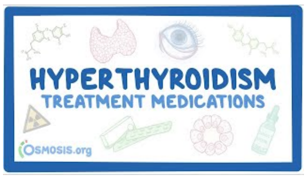
Next question

Textbooks

High-yield textbook

Extended textbook

Media


HYPERTHYROIDISM
TREATMENT MEDICATIONS
Osmosis.org

Hyperthyroidism treatment medications

Osmosis - YouTube 👍 5 👎 0

THYROID STORM

Thyroid storm

Osmosis - YouTube 👍 3 👎 2

PassMedicine

Question 103 of 414 ✗

A 55-year-old man is being reviewed ahead of discharge. He had initially presented with a 1-day history of central crushing chest pain and was diagnosed with an NSTEMI.

He had a high GRACE score so underwent an inpatient angiogram during which two stents were inserted. His baseline FBC, U&E, LFT, HbA1c and lipid profile were all normal.

What new medication should be prescribed upon discharge?

	Atorvastatin 20 mg	9%
	Atorvastatin 40 mg	18%
🟩	Atorvastatin 80 mg	70%
🟥	Simvastatin 20 mg	2%
	Simvastatin 40 mg	2%

Patients with established cardiovascular disease (e.g. IHD, stroke, PVD) should take high-intensity statin therapy (e.g. atorvastatin 80mg) regardless of baseline lipid profile

Important for me Less important

Upon discharge after receiving treatment for a myocardial infarction (MI), it is standard practice to prescribe patients a combination of five medications. This regimen typically includes dual antiplatelet therapy, which may consist of aspirin at 75 mg once daily and clopidogrel also at 75 mg once daily; a beta-blocker such as bisoprolol; an angiotensin-converting enzyme (ACE) inhibitor, for example, ramipril; and a statin, with atorvastatin being commonly used. Independent of the patient's lipid profile, high-dose statin therapy is advised for secondary prevention post-MI, specifically initiating **atorvastatin 80 mg**.

Atorvastatin 20 mg serves as primary prevention in individuals who are at elevated risk of cardiovascular events.

Atorvastatin 40 mg is not a standard dose. For secondary prevention following an MI, an 80 mg dose of atorvastatin is recommended.

Simvastatin 20 mg can be prescribed for primary prevention in those at increased risk of cardiovascular events and for the management of primary hypercholesterolaemia. However, post-MI, atorvastatin remains the preferred choice.

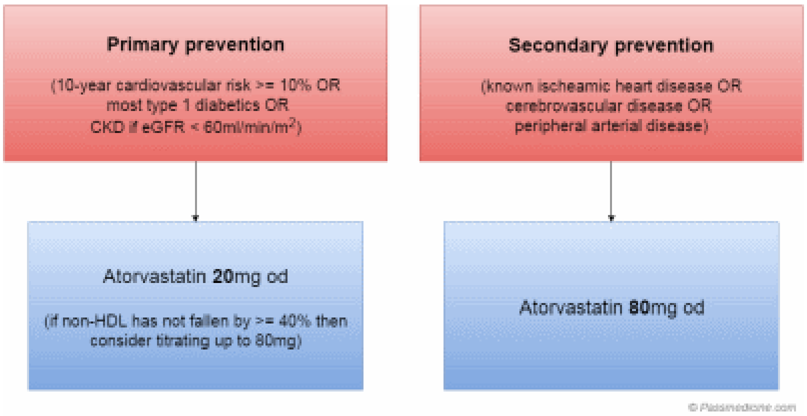
Simvastatin 40 mg might be utilised for primary prevention in patients with heightened cardiovascular risk profiles and in instances of primary hypercholesterolaemia. Nevertheless, following an MI, atorvastatin is favoured.

Discuss Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics

- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation

- smokers should be encouraged to quit

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 9 👎 6

2014 Lipid modification guidelines

Clinical Knowledge Summaries 👍 4 👎 3

Managing lipids in type 2 diabetes

Report broken link

Score: **25.2%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗

PassMedicine

Question 104 of 414 ✗

A 74-year-old male is admitted to the Emergency Department after routine blood tests by his GP showed the following results. The patient has a background of stable essential thrombocytosis.

Na+	139 mmol/l
K+	6.6 mmol/l
Urea	4.2 mmol/l
Creatinine	68 umol/l

Hb	13.5 g/dl
Plt	800 *109/l
WBC	6.6 *109/l

His ECG was normal and he was given calcium gluconate along with an insulin/dextrose infusion. Following this his potassium improved to 6.1, however over the next few days he remained persistently hyperkalaemic.

What would you suspect is the cause of his high potassium given his high cell counts?

🟩 Pseudohyperkalaemia	52%
🟥 Tumour lysis syndrome	27%
Hypomagnasaemia	8%
Conn's syndrome	8%
Chronic kidney disease	5%

High cell counts and high potassium: consider pseudohyperkalaemia

Discuss (3) Improve

Next question

Pseudohyperkalaemia ★

Pseudohyperkalaemia is a rise in serum potassium that occurs due to excessive leakage of potassium from cells, during or after blood is taken. It is a laboratory artefact and does not represent the true serum potassium concentration. The majority of potassium is intracellular and thus leakage from cells can significantly impact serum levels. In this case the potassium is released as the large numbers of platelets aggregate and degranulate.

Causes include:

- haemolysis during venipuncture (excessive vacuum of blood drawing, prolonged tourniquet use or too fine a needle gauge)
- delay in the processing of the blood specimen
- abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders)
- familial causes

Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium. For obtaining a lab sample, using a lithium heparin tube, requesting a slow spin (on the lab centrifuge) and walking the sample to the lab should ensure an accurate result.

Next question

Textbooks

High-yield textbook

PassMedicine

Question 105 of 414 ✗

Which one of the following is not associated with primary hyperparathyroidism?

Hypotension	64%
Multiple endocrine neoplasia type 1	8%
Multiple endocrine neoplasia type 2a	16%
Depression	6%
Pancreatitis	7%

The correct answer is **Hypotension**. Primary hyperparathyroidism is characterised by an excessive secretion of parathyroid hormone (PTH) from one or more of the parathyroid glands. This results in an increase in serum calcium levels, which can lead to a variety of symptoms and complications including hypertension, not hypotension. The increased calcium level causes peripheral vasoconstriction leading to raised blood pressure.

Multiple endocrine neoplasia type 1 (MEN1) is associated with primary hyperparathyroidism. MEN1 is a hereditary condition characterised by the occurrence of tumours in multiple endocrine glands, most commonly the parathyroid glands, pituitary gland, and pancreatic islet cells. Hyperparathyroidism occurs in approximately 90% of individuals with MEN1.

Similarly, **Multiple endocrine neoplasia type 2A (MEN2A)** has also been linked with primary hyperparathyroidism. MEN2A is another inherited disorder that leads to tumours in various endocrine glands such as the adrenal medulla (pheochromocytoma), thyroid gland (medullary thyroid carcinoma), and occasionally parathyroids.

Depression can be associated with primary hyperparathyroidism due to high calcium levels affecting the central nervous system function. The neuropsychiatric manifestations of hypercalcemia include depression, anxiety, cognitive dysfunction and sometimes even psychosis.

Lastly, **Pancreatitis**, both acute and chronic, can be a complication of primary hyperparathyroidism due to elevated serum calcium levels. Hypercalcemia increases pancreatic secretions and predisposes to the formation of gallstones - both factors contributing to pancreatitis.

👍 👎 Discuss (8) Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':
- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

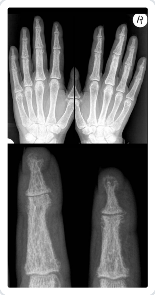
Associations
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations
- bloods
    - raised calcium, low phosphate
    - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan

- x-ray findings
    - pepperpot skull
    - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



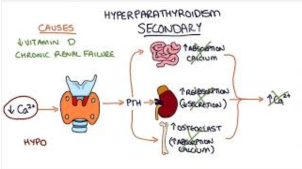
Next question

Textbooks

High-yield textbook

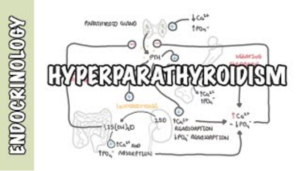
Extended textbook

Media


HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
HYPO
PTH
↑ABSORPTION CALCIUM
↑REABSORPTION (↓SECRETION)
↑OSTEOCLAST (↑ABSORPTION CALCIUM)
↑Ca2+

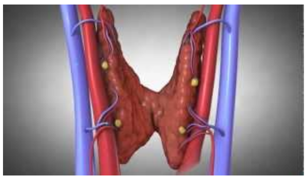
Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2



Parathyroid Glands and Hyperparathyroidism

Norman Parathyroid Center - YouTube 👍 20 👎 5

Report broken media

Score: **24.8%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗

PassMedicine

Question 106 of 414 ✗

A 61-year-old male is diagnosed with acromegaly after presenting with headaches, sweaty palms and a change in shoe size. Magnetic resonance scan has shown a pituitary macroadenoma and he is planned for transsphenoidal surgery.

What treatment is often used as an adjunct to surgery?

	Bromocriptine	17%
	Cabergoline	10%
🟩	Octreotide	53%
🟥	Pegvisomant	17%
	Prednisolone	3%

The correct answer is octreotide, a somatostatin analogue which is often used as an adjunct to surgery resulting in reduced growth hormone levels and reduction in tumour size.

Bromocriptine is a dopamine agonist used in the medical management of acromegaly. It is not commonly used as an adjunct to surgery.

Cabergoline is also a dopamine agonist. It is more commonly used in the medical management of prolactinoma as opposed to acromegaly.

Pegvisomant is a growth hormone receptor antagonist, it is useful for reducing growth hormone levels but not tumour size. For this reason, it is not the correct answer.

Prednisolone is not used as an adjunct to surgery. In some instances, steroids may be used if there were concerns over mass effect or oedema, but this is not mentioned in this stem.

Discuss (4) Improve

Next question

Acromegaly: management

Trans-sphenoidal surgery is the first-line treatment for acromegaly in the majority of patients.

If a pituitary tumour is inoperable or surgery unsuccessful then medication may be indicated:

- somatostatin analogue
    - directly inhibits the release of growth hormone
    - for example octreotide
    - effective in 50-70% of patients
- pegvisomant
    - GH receptor antagonist - prevents dimerization of the GH receptor
    - once daily s/c administration
    - very effective - decreases IGF-1 levels in 90% of patients to normal
    - doesn't reduce tumour volume therefore surgery still needed if mass effect
- dopamine agonists
    - for example bromocriptine
    - the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
    - effective only in a minority of patients

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

Next question

Textbooks

High-yield textbook

Extended textbook

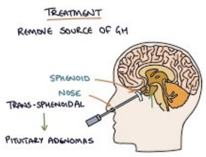
Links

Postgraduate Medical Journal 👍 7 👎 2

Modern treatment of acromegaly

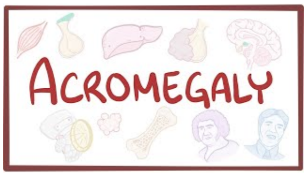
Report broken link

Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 16 👎 3


ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 8 👎 2

Report broken media

Score: **24.5%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗

PassMedicine

Question 107 of 414 ✓

A 40-year-old woman presents to her GP with discomfort in her anterior neck that she describes as a slight tightness. She does not complain of dysphagia or a hoarse voice.

On examination, she has a diffuse neck goitre that is hard on palpation, non-tender and fixed in position.

What other finding is most likely in this patient?

Highly vascularised tissue on goitre biopsy	12%
Increased vascular flow on ultrasound Doppler of the thyroid	23%
Low TSH	21%
Reduced systolic blood pressure	3%
Retroperitoneal fibrosis	42%

Riedel's thyroiditis is associated with retroperitoneal fibrosis

Important for me Less important

A hard and fixed, non-tender thyroid goitre is suggestive of Reidel's thyroiditis, also known as invasive fibrous thyroiditis. This is a rare condition characterised by a fibrotic process associated with mononuclear cell inflammation. It is associated with fibrosing conditions affecting other areas, including **retroperitoneal fibrosis** and fibrosing mediastinitis. Retroperitoneal fibrosis may not cause symptoms initially and often presents non-specifically with symptoms such as back pain and malaise. A decreased estimated glomerular filtration rate is often present.

Highly vascularised tissue on goitre biopsy would not be expected. Resected areas reveal hard, white, avascular tissue.

In Reidel's thyroiditis, it is often found there is decreased, rather than **increased vascular flow on ultrasound Doppler of the thyroid** due to fibrous infiltration.

Most patients are euthyroid and some are hypothyroid. Therefore, a **low TSH** would not be an expected finding.

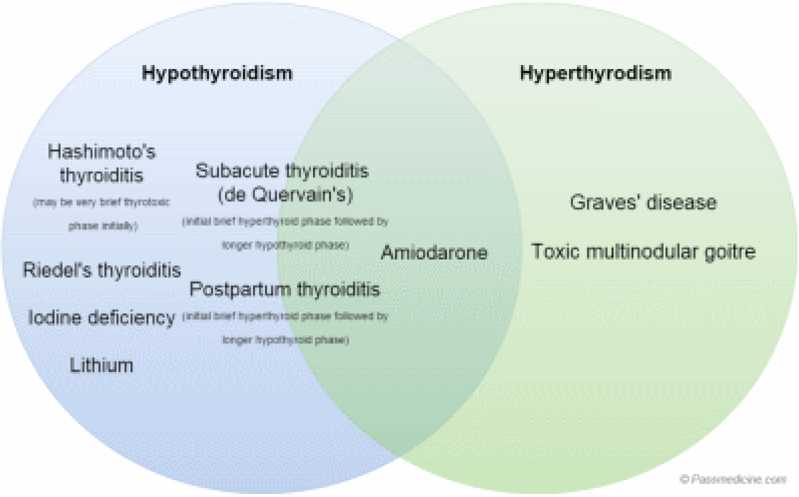
Retroperitoneal fibrosis can involve the renal arteries. This means in this patient, hypertension would be much more likely than a **reduced systolic blood pressure**.

Discuss (4) Improve

Next question

Riedel's thyroiditis

Riedel's thyroiditis is a rare cause of hypothyroidism characterised by dense fibrous tissue replacing the normal thyroid parenchyma. On examination a hard, fixed, painless goitre is noted. It is usually seen in middle-aged women. It is associated with retroperitoneal fibrosis.


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Graves' disease
Toxic multinodular goitre
Riedel's thyroiditis
Postpartum thyroiditis
Iodine deficiency
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Lithium
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

Textbooks

PassMedicine

Question 108 of 414 ✗

A 43-year-old woman is referred to the medical unit with vomiting, dizziness, and abdominal pain. She has a background of coeliac disease.

There is mild generalized abdominal tenderness but no guarding or rigidity on examination. The palmar creases are noted to be pigmented. The blood pressure is 88/54 mmHg. She is afebrile.

What test is likely to be diagnostic?

	9am cortisol	13%
🟩	ACTH stimulation test	66%
	CT abdomen with contrast	5%
	Dexamethasone suppression test	15%
🟥	Procalcitonin	1%

The short synacthen test is the best test to diagnose Addison's disease

Important for me Less important

ACTH stimulation test is correct. The patient presents with vomiting, abdominal pain, and hypotension. This has a broad differential. However, the pigmented palmar creases suggest Addison's disease as the cause. It is caused by the stimulant effect of excess adrenocorticotrophic hormone (ACTH) on the melanocytes to produce melanin. Addison's disease is associated with other autoimmune conditions like coeliac disease. The ACT stimulation test is also known as the short synacthen test. In this test, an early morning cortisol is checked and synthetic ACTH is subsequently administered. An appropriate increment in cortisol secretion is then sought.

9am cortisol is incorrect.This is a screening test for hypoadrenalism and if low should prompt a short synacthen test which is diagnostic of Addison's disease.

CT abdomen with contrast is incorrect. It would not be unreasonable to do this test in someone presenting with abdominal pain and low blood pressure to exclude life-threatening diagnoses. However, the history suggests Addison's disease for reasons outlined so it is likely to exclude relevant diagnoses rather than confirm the suspected diagnosis.

Dexamethasone suppression test is incorrect. This test is used to confirm a diagnosis of Cushing's syndrome. This is essentially the opposite of Addison's in that it causes an excess of cortisol rather than hypocortisolaemia. Hypertension rather than hypotension is a feature of cortisol excess. This is therefore incorrect.

Procalcitonin is incorrect. If raised, this suggests a bacterial infection. The pigmented palmar creases and absence of fever suggest Addison's rather than bacterial sepsis as a cause of the presentation. Additionally, procalcitonin is neither perfectly sensitive nor specific for sepsis. Therefore, even if it was positive it would not be 'diagnostic' of sepsis per se but rather simply supportive in the correct clinical context. This is therefore incorrect.

Discuss Improve

Next question

Addison's disease: investigations

In a patient with suspected Addison's disease the definite investigation is an ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If an ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:

- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 6 👎 4

2017 Adrenal insufficiency â€“ recognition and management

Report broken link

Media

Primary adrenal insufficiency (Addison's disease)

Osmosis - YouTube 👍 22 👎 8

Addison's disease

Armando Hasudungan - YouTube 👍 12 👎 5

Report broken media

Score: **25%**

1 ✓

2 ✓

PassMedicine

← Question 109 of 414 ✓ →

A 35-year-old female has recently been diagnosed with Addison's disease due to autoimmune adrenal failure after presenting with a 3-month history of lethargy, nausea, weight loss and fainting. Which of the following physical signs may you find in this patient?

Stretch marks on her abdomen	12%
Multiple bruises on her limbs	12%
Frontal balding	10%
Thinning of the axillary hair	49%
Cafe au lait spots	17%

Thinning of pubic and axillary hair is seen in females with Addison's disease due to reduced production of testosterones from the adrenal gland

Important for me Less important

The correct answer is thinning of the axillary hair. The patient has failure of the adrenal gland due to autoimmune attack. As well as deficiency of glucocorticoids and mineralocorticoids, she will have lower levels of androgens, which are usually produced in females by the zona reticularis of the adrenal cortex. This leads to thinning of hair grown at puberty, which is androgen dependent. The scalp hair is unaffected.

Stretch marks, skin thinning, easy bruising and poor wound healing are found in Cushing's disease or in patients given longterm exogenous steroids. Cafe au lait spots are seen in neurofibromatosis type I.

NICE CKS. Addison's disease.

Discuss (2) Improve

Next question

Addison's disease ★

Autoimmune destruction of the adrenal glands is the most common cause of primary hypoadrenalism in the UK, accounting for 80% of cases. This is termed Addison's disease and results in reduced cortisol and aldosterone being produced.

Features

- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases)
    - ACTH is derived from a larger precursor molecule called proopiomelanocortin (POMC). When POMC is cleaved to produce ACTH, other melanocyte-stimulating hormones (MSH) are also produced. These MSHs have the effect of stimulating melanocytes in the skin to produce more melanin, the pigment responsible for skin colour
    - primary Addison's is associated with hyperpigmentation whereas secondary adrenal insufficiency is not
- vitiligo
- loss of pubic hair in women
- hypotension
- hypoglycaemia
- hyponatraemia and hyperkalaemia may be seen
- crisis: collapse, shock, pyrexia

Other causes of hypoadrenalism

Primary causes

- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

Secondary causes

- pituitary disorders (e.g. tumours, irradiation, infiltration)

Exogenous glucocorticoid therapy

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 2 👎 0

Addison's disease

Royal College of Physicians 👍 4 👎 2

2017 Adrenal insufficiency â€“ recognition and management

Report broken link

Media

ADDISON'S DISEASE
ADDISONS DISEASE

Addison's disease

Armando Hasudungan - YouTube 👍 30 👎 2

Primary adrenal insufficiency (Addison's disease)

Osmosis - YouTube 👍 13 👎 5

PassMedicine

Question 110 of 414 ✗

A 54-year-old woman presents to the Emergency Department with confusion and fever. She has a past history of thyrotoxicosis previously treated with radioiodine therapy. On examination she has a pulse of 120/min regular, blood pressure 150/90 mmHg, temperature of 39.1ºC and a respiratory rate of 18/min. Examination of the cardiorespiratory system is unremarkable and urine dipstick is clear. Blood results showed the following:

Free T4	84 pmol/l (normal range 10-22 pmol/l)
Free T3	29 pmol/l (2.5-5.5 pmol/l)
TSH	< 0.01 mU/l (0.5-4.0 mU/l)

Which one of the following does not have a role in the subsequent management?

	Lugol's iodine	12%
🟥	Propranolol	3%
	Propylthiouracil	6%
🟩	Bicarbonate	70%
	Dexamethasone	9%

The correct answer is **Bicarbonate**. This patient's presentation and blood results are suggestive of a thyroid storm, which is a life-threatening exacerbation of thyrotoxicosis. Management of thyroid storm involves multiple strategies including beta-blockers to control symptoms (such as tachycardia), antithyroid drugs to reduce new hormone synthesis, iodine solution (Lugol's iodine) to block the release of thyroid hormones, and glucocorticoids (dexamethasone) to decrease peripheral conversion of T4 to the more potent T3. Bicarbonate does not have a role in the management of thyroid storm.

Lugol's iodine is used in the treatment of thyroid storm to inhibit the release of preformed thyroid hormone from the gland. It also decreases the size and vascularity of the gland, making surgery safer if needed.

Propranolol, a non-selective beta-blocker, has two roles in this setting. Firstly, it helps control symptoms such as palpitations, tremor and anxiety caused by increased beta-adrenergic tone.

Secondly, it inhibits the peripheral conversion of T4 to T3.

Propylthiouracil is an antithyroid drug that inhibits new hormone synthesis by blocking the enzyme thyroperoxidase. It also blocks the peripheral conversion of T4 to T3.

Dexamethasone reduces peripheral conversion of T4 to T3 and may also decrease autoantibody production in Graves' disease - one possible cause of thyrotoxicosis.

In contrast, **bicarbonate** is used for metabolic acidosis correction but it doesn't have any specific role in managing thyroid storm or its complications. Therefore, it doesn't contribute directly towards controlling this patient's condition.

👍 👎 💬 Discuss (11) Improve

Next question

Thyroid storm ★

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating events:

- thyroid or non-thyroidal surgery
- trauma
- infection
- acute iodine load e.g. CT contrast media

Clinical features include:

- fever > 38.5ºC
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test - jaundice may be seen clinically

Management:

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- beta-blockers: typically IV propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

Next question

Textbooks

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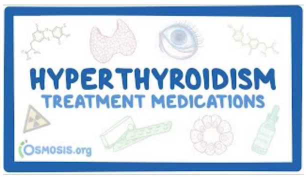
HYPERTHYROIDISM
TREATMENT MEDICATIONS
Osmosis.org

Hyperthyroidism treatment medications

Osmosis - YouTube 👍 5 👎 0

THYROID
STORM

Thyroid storm

Osmosis - YouTube 👍 3 👎 2

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Question 111 of 414 ✗

A 66-year-old lady with a long history of poorly controlled type-2 diabetes is started on a new medication. She is told it works by increasing urinary glucose excretion and the doctor says it is an SGLT-2 inhibitor.

Which of the following medications is in this drug class?

	Tolbutamide	1%
🟩	Dapagliflozin	91%
	Exenatide	2%
🟥	Linagliptin	5%
	Pioglitazone	2%

Gliflozins - SGLT2 inhibitors

Important for me Less important

Gliflozins are SGLT2 inhibitors.

Tolbutamide is a sulfonylurea.

Exenatide is a GLP-1 receptor agonist.

Linagliptin is a DPP-4 inhibitor.

Pioglitazone is a thiazolidinedione.

Discuss (4) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

Textbooks

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BNF 👍 3 👎 9

Dapagliflozin

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Media

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Question 112 of 414

A 47-year-old male visits the GP for review and a routine blood check. He has a past medical history of angina, hypertension, asthma and hyperlipidaemia. You look to his medications which shows an extensive polypharmacy including fenofibrate. This drug lowers triglyceride levels and increases high-density lipoprotein (HDL) synthesis.

What is the mechanism of this drug?

Inhibition of hepatic diacylglycerol acyltransferase-2	7%
HMG-CoA reductase inhibitor	10%
Activation of PPAR receptor resulting in increase lipoprotein lipase (LPL) activity	65%
Reduction in the reabsorption of bile acids	9%
Increased production of apolipoprotein E by the liver	9%

Fibrates work through activating PPAR alpha receptors resulting in an increase in LPL activity reducing triglyceride levels

Important for me Less important

Fibrates are cholesterol-lowering drugs that work through activating PPAR alpha receptors resulting in an increase in LPL activity. LPL increases the uptake of triglyceride fatty acids in muscles resulting in lower levels in the blood.

Statins inhibit HMG-CoA reductase resulting in the reduction of the mevalonate pathway leading to reduced cholesterol levels.

Niacin or nicotinic acid (vitamin B3) inhibits hepatic diacylglycerol acyltransferase-2 which is required for triglyceride synthesis.

Bile acid sequestrants are a class of drugs which work by binding to bile salts reducing reabsorption of bile acids.

Apolipoprotein E is a protein involved in the metabolism of fats it specifically removes chylomicron remnants.

Discuss (2) Improve

Next question

Fibrates

Fibrates are used in the management of hyperlipidaemia, particularly raised triglycerides.

Fibrates work through activating PPAR alpha receptors resulting in an increase in LPL activity reducing triglyceride levels.

Adverse effects:

- gastrointestinal side-effects are common
- increased risk of thromboembolism

Next question

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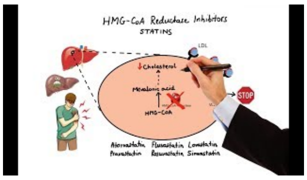
HMG-CoA Reductase Inhibitors
STATINS
LDL
↓Cholesterol
Mevalonic acid
HMG-CoA
STOP
Atorvastatin Fluvastatin Lovastatin
Pravastatin Rosuvastatin Simvastatin

Drugs for hyperlipidaemia

PassMedicine

Question 113 of 414 ✗

A 33-year-old woman who is known to have familial hypercholesterolaemia comes for review. She is planning to have children and asks for advice regarding medication as she currently takes atorvastatin 80mg on. What is the most appropriate advice?

	Switch to atorvastatin 10mg	1%
	Continue current drug at same dose	24%
🟩	Stop atorvastatin before trying to conceive	53%
	Switch to ezetimibe	16%
🟥	Switch to simvastatin 40mg	5%

Statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Discuss (3) Improve

Next question

Familial hypercholesterolaemia ★

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Case finding:

- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
    - a total cholesterol level greater than 7.5 mmol/l and/or
    - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:

    - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
    - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Next question

Textbooks

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Links

The FH Foundation 👍 3 👎 1

Simon Broom Criteria

The FH Foundation 👍 3 👎 1

High cholesterol during preganancy

NICE 👍 3 👎 1

2008 Familial hypercholesterolaemia guidelines

Public Library of Science (PLoS) 👍 2 👎 1

Cascade Screening for Familial Hypercholesterolemia (FH)

Report broken link

Media

FAMILIAL
HYPERCHOLESTEROLEMIA
OSMOSIS.org

Familial hypercholesterolaemia

Osmosis - YouTube 👍 20 👎 1

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Score: **24.8%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗

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Question 114 of 414 ✗

A diabetic man is diagnosed as having painful diabetic neuropathy in his feet. He has no other medical history of note. What is the most suitable first-line treatment to relieve his pain?

🟩	Duloxetine	82%
	Sodium valproate	1%
	Carbamazepine	9%
	Referral to pain management clinic	4%
🟥	Tramadol	5%

The correct answer is **Duloxetine**. According to the National Institute for Health and Care Excellence (NICE) guidelines, Duloxetine is one of the first-line treatments for painful diabetic neuropathy. It works by inhibiting the reuptake of serotonin and norepinephrine in the central nervous system, thereby increasing their concentration and enhancing pain suppression.

Sodium valproate is not a recommended treatment for painful diabetic neuropathy. It is an antiepileptic drug that stabilises electrical activity in the brain. While it has been used off-label for various types of neuropathic pain, its use in diabetic neuropathy lacks robust evidence and therefore it's not considered a first-line option.

Carbamazepine is another antiepileptic medication that isn't typically used as a first-line treatment for this condition. Its main indication is in treating seizures and certain types of nerve pain such as trigeminal neuralgia but it's not commonly used or recommended for diabetic neuropathy.

A **referral to a pain management clinic** could be considered if first-line treatments are ineffective or contraindicated. However, it would not be the most suitable initial step according to NICE guidelines which recommend starting with pharmacological options like Duloxetine or Pregabalin.

Finally, **Tramadol** might be used as a second-line treatment when other medications have failed or cannot be tolerated due to side effects. Tramadol is a strong opioid analgesic that works by binding to mu-opioid receptors and inhibiting reuptake of norepinephrine and serotonin, but its potential for addiction and withdrawal symptoms make it less favourable as an initial option.

Discuss (3) Improve

Next question

Diabetic neuropathy

Peripheral neuropathy

Diabetes typically leads to sensory loss and not motor loss. Sensory loss typically results in a 'glove and stocking' distribution, with the lower legs affected first due to the length of the sensory neurons supplying this area. Painful diabetic neuropathy is also a common problem in clinical practice.

NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:
- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

Gastrointestinal autonomic neuropathy

Gastroparesis
- occurs secondary to autonomic neuropathy
- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

Chronic diarrhoea
- often occurs at night

Gastro-oesophageal reflux disease
- caused by decreased lower esophageal sphincter (LES) pressure

PassMedicine

Question 115 of 414 ✗

A 35-year-old gentleman is followed up in general practice after a routine health check at work has identified high blood pressure. He has been started on initial anti-hypertensive therapy whilst awaiting investigation. He is otherwise well with no past medical history of note.

He reports that his grandfather had been previously diagnosed with Conn's syndrome at an early age.

Which of the following can interfere with testing for primary hyperaldosteronism?

Digoxin	8%
Amlodipine	5%
Ivabradine	6%
Bisoprolol	7%
Ramipril	74%

The answer here is ramipril. The reason behind this is due to its interference with the renin-angiotensin-aldosterone system, for which the other medications do not.

Medications that can cause false negative renin:aldosterone ratio results are the following:
- Angiotensin-converting enzyme inhibitors (e.g. ramipril or lisinopril).
- Angiotensin receptor blockers (e.g. losartan).
- Direct renin inhibitors (e.g aliskiren).
- Aldosterone antagonists (e.g. spironolactone or eplerenone).

Discuss (8) Improve

Next question

Primary hyperaldosteronism

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes

- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

Features

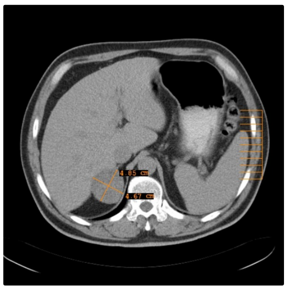
- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
  - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone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4.67 cm

Next question

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Links

The Endocrine Society 👍 5 👎 3

2016: The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment

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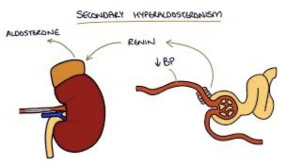
Media


SECONDARY HYPERALDOSTERONISM
ALDOSTERONE
RENIN
↓BP

Hyperaldosteronism and Conn's Syndrome

Zero To Finals - YouTube 👍 47 👎 5

PassMedicine

Question 116 of 414 ✓

A 56-year-old man is reviewed in the Cardiology outpatient clinic following a myocardial infarction one year previously. During his admission he was found to be hypertensive and diabetic. He complains that he has put on 5kg in weight in the past 6 months. Which of his medications may be contributing to his weight gain?

Metformin	4%
Losartan	1%
Clopidogrel	1%
Gliclazide	93%
Simvastatin	1%

Sulfonylureas often cause weight gain

Important for me Less important

The correct answer is **Gliclazide**. Gliclazide is a sulfonylurea, which is a class of oral hypoglycemic agents used in the management of type 2 diabetes mellitus. Sulfonylureas work by stimulating insulin release from pancreatic beta cells. One of the side effects of this class of drugs, including gliclazide, is weight gain. This occurs due to increased insulin levels leading to increased glucose uptake and storage as glycogen or fat.

Metformin is an incorrect answer because it is an oral antidiabetic agent that works by reducing hepatic glucose production and increasing peripheral glucose uptake and utilization. Metformin does not cause weight gain; in fact, it may lead to modest weight loss in some patients.

Losartan is also an incorrect answer. Losartan is an angiotensin II receptor blocker (ARB) used for treating hypertension. ARBs work by blocking the binding of angiotensin II to its receptors, resulting in vasodilation and reduced aldosterone secretion. Losartan does not typically cause weight gain as a side effect.

Clopidogrel is another incorrect answer. Clopidogrel is an antiplatelet drug that works by inhibiting platelet aggregation through irreversible blockade of adenosine diphosphate (ADP) receptors on platelets. It is commonly prescribed following a myocardial infarction to reduce the risk of further cardiovascular events, but it does not contribute to weight gain.

Finally, **Simvastatin** is also an incorrect answer. Simvastatin belongs to the statin class of drugs, which are lipid-lowering medications that inhibit the enzyme HMG-CoA reductase involved in cholesterol synthesis. Statins are used for primary and secondary prevention of cardiovascular disease. Weight gain is not a common side effect of simvastatin or other statin medications.

Discuss (3) Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects
- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects
- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

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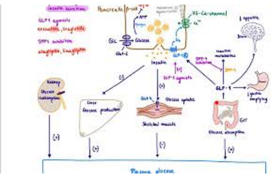
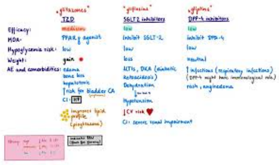


Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10



Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

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Score: **25%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

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Question 117 of 414

A 62-year-old man with mixed hyperlipidaemia, hypertension and ischaemic heart disease comes to the clinic for review. He has suffered a left lower limb deep vein thrombosis and been started on rivaroxaban for 3 months as treatment. there are no apparent risk factors for deep vein thrombosis and he has been fit and active, still working as a landscape gardener.

Which of the following medications that he takes may be associated with increased risk of deep vein thrombosis?

	Ramipril	3%
	Atorvastatin	5%
🟩	Fenofibrate	65%
	Bisoprolol	4%
🟥	Indapamide	23%

Fibrates may increase the risk of venous thromboembolism

Important for me Less important

Questions were raised as to whether fibrates may be associated with venous thromboembolism after an imbalance in favour of comparator therapies with respect to thromboembolic events. A meta-analysis has now suggested that this imbalance may represent a real risk of VTE in patients prescribed fibrates: (OR, 1.58; 95% CI, 1.23-2.02).

https://academic.oup.com/eurheartj/article/31/10/1248/486868

The data from the same meta-analysis for statins suggests, although does not confirm, that they may be associated with reduced risk of venous thromboembolism: (OR, 0.81; 95% CI, 0.66-0.99), although the statin data was very heterogenous and may not therefore represent a real finding. Beta-blockers, thiazide like diuretics and ACE inhibitors are thought to have no impact on risk of venous thromboembolism.

Discuss (3) Improve

Next question

Fibrates ★

Fibrates are used in the management of hyperlipidaemia, particularly raised triglycerides.

Fibrates work through activating PPAR alpha receptors resulting in an increase in LPL activity reducing triglyceride levels.

Adverse effects:
- gastrointestinal side-effects are common
- increased risk of thromboembolism

Next question

Textbooks

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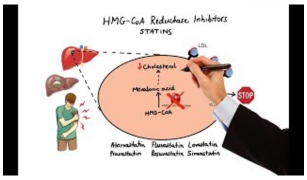
HMG-CoA Reductase Inhibitors
STATINS
LDL
↓Cholesterol
Mevalonic acid
HMG-CoA
STOP
Atorvastatin Fluvastatin Lovastatin
Pravastatin Rosuvastatin Simvastatin

Drugs for hyperlipidaemia

Speed Pharmacology - YouTube 👍 27 👎 1

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PassMedicine

← Question 118 of 414 ✗ →

A 24-year-old woman attends the diabetic clinic for an annual review. She was diagnosed with type 1 diabetes mellitus at 14 years of age. She has advised you that she has been gaining weight recently and her BMI is currently 28 kg/m^2. Her blood pressure is 135/85 mmHg.

Blood results are as follows:

Hb	125 g/L	Male: (135-180) Female: (115 - 160)
Platelets	188 * 10^9/L	(150 - 400)
WBC	6.8 * 10^9/L	(4.0 - 11.0)
Na^+	136 mmol/L	(135 - 145)
K^+	4.2 mmol/L	(3.5 - 5.0)
Urea	4.8 mmol/L	(2.0 - 7.0)
Creatinine	68 µmol/L	(55 - 120)

HbA1c	50 mmol/mol	(<48)
Urinary ACR	45 mg/mmol	(<3)

What treatment is indicated?

	Gliclazide	6%
🟩	Metformin	49%
	No changes required	8%
	Orlistat	5%
🟥	Ramipril	32%

Patients with type I diabetes and a BMI > 25 should be considered for metformin in addition to insulin

Important for me Less important

Metformin is correct. The patient's HbA1c is slightly above the target of 48 mmol/mol (6.5%). Metformin should be considered in addition to insulin therapy for adults with type 1 diabetes if they have a BMI of 25 kg/m2 or above (23 kg/m2 or above for people from South Asian and related family backgrounds). This is because overweight and obese patients will also likely have a degree of insulin resistance. Metformin can also have other long-term health benefits including lowering cholesterol levels and reducing heart disease risk. In this case, metformin will have a good chance of improving their blood glucose control while minimising her effective insulin dose.

Gliclazide is incorrect. This medicine is not used to treat type 1 diabetes.

No changes required is incorrect. As stated above, metformin should be considered given the patient's significantly elevated BMI and raised HbA1c.

Orlistat is incorrect. Orlistat is a lipase inhibitor which reduces the absorption of dietary fat. It can be used to help with weight loss. Orlistat has many side effects and can cause liver disease. Therefore in the first instance, a healthy diet and regular physical activity to manage weight is recommended.

Ramipril is incorrect. In adults with type 1 diabetes, blood pressure targets are governed by urine albumin:creatinine ratio (ACR) as follows:

- For adults with an ACR less than 70 mg/mmol, aim for a clinic systolic blood pressure less than 140 mmHg (target range 120 to 139 mmHg) and a clinic diastolic blood pressure less than 90 mmHg.
- For adults with an ACR of 70 mg/mmol or more, aim for a clinic systolic blood pressure less than 130 mmHg (target range 120 to 129 mmHg) and a clinic diastolic blood pressure less than 80 mmHg.

The patient in this case has an ACR of 45 mg/mmol, and thus a BP target of <140/90. Since her blood pressure is 135/85, no anti-hypertensives are required at the current time.

👍 👎 💬 Discuss (6) Improve

Next question

Diabetes mellitus: management of type 1 ★

The long-term management of type 1 diabetics is an important and complex process requiring the input of many different clinical specialties and members of the healthcare team. A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

NICE released guidelines on the diagnosis and management of type 1 diabetes in 2015. We've only highlighted a very select amount of the guidance here which will be useful for any clinician looking after a patient with type 1 diabetes.

HbA1c
- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

Self-monitoring of blood glucose
- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

Blood glucose targets
- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

Type of insulin
- offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

Metformin
- NICE recommend considering adding metformin if the BMI >= 25 kg/m^2

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 4 👎 2

2015 Type 1 diabetes in adults: diagnosis and management

NICE 👍 3 👎 2

2015 Diabetes (type 1 and type 2) in children and young people

Report broken link

Score: **24.6%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓

PassMedicine

Question 119 of 414 ✗

A 14-year-old boy presents to his GP with polyuria, polydipsia, fatigue and weight loss. He is diagnosed with diabetes mellitus and started on insulin. Three months later he presents to the Emergency Department in a non-ketotic hyperglycaemic state.

On reviewing his history, the diabetes team find that his mother was also diagnosed with diabetes aged 14. He is switched to gliclazide.

Given the likely diagnosis, what is the inheritance pattern of this condition?

🟩	Autosomal dominant	79%
	Autosomal recessive	8%
	Mitochondrial inheritance	6%
🟥	X-linked dominant	5%
	X-linked recessive	2%

MODY is inherited in an autosomal dominant fashion so a family history is often present

Important for me Less important

The history here is pointing towards maturity-onset diabetes of the young (MODY) - which is often misdiagnosed as type 1 diabetes mellitus initially, as is the case in this scenario. The patient was started on an insulin regime but later, during an emergency, found to be non-ketotic. This, along with family history, is indicative of the diagnosis actually being MODY, as well as the change from insulin to gliclazide. It is inherited in an autosomal dominant fashion.

The other inheritance modes are therefore incorrect.

Discuss (4) Improve

Next question

MODY ★

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **24.4%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗

PassMedicine

Question 120 of 414 ✗

Tabitha is a 78-year-old woman who presents with urinary incontinence. Her incontinence has been ongoing for the past 2 years with no relief. Her symptoms usually occur on laughing and coughing. She has not experienced any episodes of nocturia. She also has not experienced a strong need to pass urine prior to her incontinence.

She has tried pelvic floor exercises and reducing caffeine intake but these failed to improve her symptoms.

Her urinalysis today shows no leukocytes or nitrites. A pelvic examination does not show any evidence of uterine prolapse. On consultation, she declines any surgical intervention.

What is the next most appropriate intervention for her incontinence?

🟩	Duloxetine	69%
	Mirabegron	15%
	Oxybutynin	11%
🟥	Solifenacin	2%
	Tolterodine	2%

Duloxetine may be used in patients with stress incontinence who don't respond to pelvic floor muscle exercises and decline surgical intervention

Important for me Less important

Her symptoms suggests her incontinence is likely due to stress incontinence. It is important to rule out other causes such as infection as the underlying cause for urinary incontinence prior to embarking on further treatment.

Medical management should be trialled when non-pharmacological management fails. This normally involves pelvic floor exercises and reduction in dietary caffeine.

Medical management of stress incontinence is duloxetine. This acts as a serotonin/norepinephrine reuptake inhibitor and its common side effects include nausea, dizziness and insomnia.

Oxybutynin, tolterodine, and solifenacin are often used as 1st-line treatment for urge incontinence and are all antimuscarinic agents. Should these therapies fail, mirabegron, an β3 agonist, can be used as a 2nd-line therapy.

Discuss (3) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation
- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture

- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

Report broken link

Media

URINARY INCONTINENCE

Urinary incontinence

Osmosis - YouTube 👍 0 👎 1

Report broken media

Score: **24.2%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗
12 ✓
13 ✗
14 ✓
15 ✗

PassMedicine

Question 121 of 414 ✗

A 59-year-old man presents to the Acute Medical Unit complaining of back pain. He has a history of hypertension, congestive cardiac failure, type 2 diabetes and prostate cancer.

His blood pressure is well-controlled on amlodipine and ramipril. In addition to this, he takes bisoprolol and eplerenone due to previous issues with lower limb swelling. He takes metformin, and was prescribed sitagliptin two months ago due to an increase in his Hba1c readings. An isotope bone scan four months before had shown metastasis of his prostate cancer to his pelvic girdle, at which point he had commenced monthly goserelin injections.

On examination, you notice pronounced breast tissue bilaterally.

Which of his medications is the most likely cause of this examination finding?

	Eplerenone	22%
	Ramipril	2%
🟥	Metformin	1%
	Sitagliptin	2%
🟩	Goserelin	73%

GnRH agonists (e.g. goserelin) used in the management of prostate cancer may result in gynaecomastia

Important for me Less important

This patient has an incidental examination finding of gynaecomastia. Of the medications listed above, goserelin is most strongly linked to causing gynaecomastia.

Goserelin is a gonadotropin releasing hormone (GnRH) agonist. In normal physiology, the pulsatile release of GnRH stimulates testosterone production. When goserelin is given long-term in a non-pulsatile manner, this disrupts the endogenous feedback loops controlling testosterone production, and results in hypoandrogenism. This in turn causes the development of gynaecomastia.

Of note, although both are aldosterone antagonists, a comparison of results from the RALES and EPHESUS trials revealed that eplerenone was much less likely to cause gynaecomastia than spironolactone in heart failure patients (0.5% vs 10%). This is because unlike spironolactone, eplerenone does not inhibit free testosterone binding to androgen receptors on breast tissue.

The other three medications listed are not strongly linked to the development of gynaecomastia.

Discuss (2) Improve

Next question

Gynaecomastia

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia
- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia
- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia
- tricyclics

- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **24%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓

PassMedicine

← Question 122 of 414 ✗ ⚐ →

A 72-year-old woman presents with polyuria and polydipsia. Investigations reveal the following:

Fasting glucose	4.5 mmol/l
Calcium	2.88 mmol/l
Phosphate	0.75 mmol/l
Parathyroid hormone	6 pmol/L (normal range = 0.8 - 8.5)

What is the most likely underlying diagnosis?

	Myeloma	15%
	Sarcoidosis	7%
🟩	Primary hyperparathyroidism	63%
🟥	Vitamin D excess	9%
	Osteomalacia	7%

The PTH level in primary hyperparathyroidism may be normal

Important for me Less important

Despite a raised calcium level the parathyroid hormone level is inappropriately normal. This points towards a diagnosis of primary hyperparathyroidism and the other causes (such as myeloma) would lead to a suppression of parathyroid hormone

👍 👎 Discuss (9) Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism

- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':

- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II

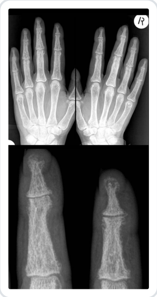
Investigations

- bloods
  - raised calcium, low phosphate
  - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
  - pepperpot skull
  - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-

organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



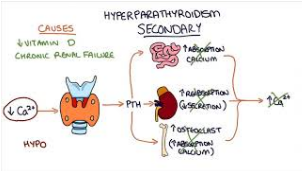
Next question

Textbooks

High-yield textbook

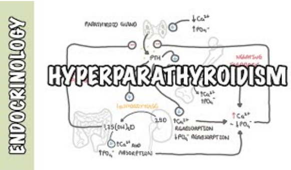
Extended textbook

Media


HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
HYPO
PTH
↑ABSORPTION CALCIUM
↑REABSORPTION (↓SECRETION)
↑OSTEOCLAST (↑ABSORPTION CALCIUM)
↑Ca2+

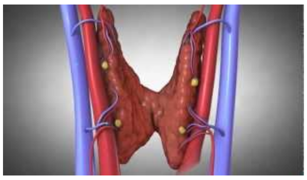
Understanding Hyperparathyroidism

Zero to Finals - YouTube 70 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2



Parathyroid Glands and Hyperparathyroidism

Norman Parathyroid Center - YouTube 👍 20 👎 5

Report broken media

Score: **23.8%**

1	✓
2	✓
3	✓
4	✗
5	✗
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9	✓
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12	✓
13	✗
14	✓
15	✗
16	✗
17	✓

PassMedicine

Question 123 of 414 ✓

A 20-year-old woman with a history of type 1 diabetes since the age of 8 comes to the Emergency department with nausea, vomiting, weight loss and frequent episodes of hypoglycaemia. She has been treated with a basal bolus regime of insulin since diagnosis and usually has very stable diabetes control. On examination, her blood pressure is 105/70 mmHg with a postural drop of 15 mmHg. Her pulse is 74 beats per minute and regular. Her body mass index is 21 kg/m^2.

Investigations

Na^+	127 mmol/l
K^+	5.0 mmol/l
Urea	11.2 mmol/l
Creatinine	122 µmol/l
Glucose	4.8 mmol/l
TSH	10.2 IU/l
Free thyroxine	7 pmol/l

Which of the following is the most important intervention?

Fluid restriction	5%
[✓ IV hydrocortisone]	54%
IV normal saline	26%
Oral fludrocortisone	5%
Oral thyroxine	10%

The hyponatraemia and potassium towards the upper end of the normal range, coupled with hypoglycaemia, fit well with a diagnosis of Addison's disease. Although features of hypothyroidism may co-exist with hypoadrenalism, corticosteroid replacement is the most important first step in therapy because commencing thyroxine may worsen any adrenal crisis.

Fluid restriction is not appropriate given signs of volume depletion and the likelihood of Addison's being the primary diagnosis. Although fluid replacement with normal saline may be useful in relieving symptoms of volume depletion, it is unlikely to be effective without commencing hydrocortisone therapy. Oral fludrocortisone is added to hydrocortisone in patients who are corticosteroid replete but still suffer from symptoms of hyponatraemia or volume depletion.

👍 👎 Discuss (11) Improve

Next question

Addison's disease ★

Autoimmune destruction of the adrenal glands is the most common cause of primary hypoadrenalism in the UK, accounting for 80% of cases. This is termed Addison's disease and results in reduced cortisol and aldosterone being produced.

Features
- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases)
  - ACTH is derived from a larger precursor molecule called proopiomelanocortin (POMC). When POMC is cleaved to produce ACTH, other melanocyte-stimulating hormones (MSH) are also produced. These MSHs have the effect of stimulating melanocytes in the skin to produce more melanin, the pigment responsible for skin colour
  - primary Addison's is associated with hyperpigmentation whereas secondary adrenal insufficiency is not
- vitiligo
- loss of pubic hair in women
- hypotension
- hypoglycaemia
- hyponatraemia and hyperkalaemia may be seen
- crisis: collapse, shock, pyrexia

Other causes of hypoadrenalism

Primary causes
- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

Secondary causes

- pituitary disorders (e.g. tumours, irradiation, infiltration)

Exogenous glucocorticoid therapy

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 2 👎 0

Addison's disease

Royal College of Physicians 👍 4 👎 2

2017 Adrenal insufficiency â€“ recognition and management

Report broken link

Media

ADDISON'S DISEASE

Addison's disease

Armando Hasudungan - YouTube

PassMedicine

Question 124 of 414 ✗

A 62-year-old man presents for review of his type 2 diabetes. He has been found to have HbA1c levels of 62mmol/mol despite metformin therapy. You decide to commence him on sitagliptin for dual hypoglycaemic therapy.

What is the mechanism of this drug?

Decreases GLP-1 breakdown	61%
Decreases levels of GIP incretins	13%
Increases GLP-1 production	11%
Increases insulin secretion from the pancreas	7%
Mimics GLP-1	8%

DPP-4 inhibitors increase levels of incretins such as GLP-1 and GIP

Important for me Less important

Decreases GLP-1 breakdown is the correct answer. By blocking the DPP-4 enzyme, sitagliptin reduces the peripheral breakdown of GLP-1 and GIP. This potentiates the incretin effect which is typically reduced in diabetes.

Decreases levels of GIP incretins is incorrect, as DPP-4 inhibitors block the enzyme which breaks down GLP-1 and GIP which results in higher levels of GIP incretins, rather than lower.

Increases GLP-1 production is incorrect, as DPP-4 inhibitors block the enzyme which breaks down GLP-1 and GIP but they do not directly increase the production of GLP-1.

Increases insulin secretion is the mechanism of secretagogues, such as sulfonylureas, and not of DPP-4 inhibitors such as sitagliptin.

Mimics GLP-1 is the mechanism of action of incretin analogues, such as exenatide, and not of DPP-4 inhibitors.

Discuss (1) Improve

Next question

Diabetes mellitus: GLP-1 drugs

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points
- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

High-yield textbook

Extended textbook

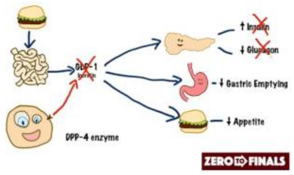
Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

Report broken link

Media


GLP-1 release
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

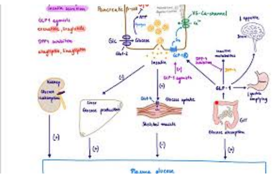
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2

The role of "GLP" system in tt of diabetes
Sitagliptin
(-)
inactive GLP-1
DPP-4
incretin
"GLP-1"
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 26 👎 5

PassMedicine

Question 125 of 414 ✗

A 44-year-old woman attends a medication review with her general practitioner. She reports a weight gain of 10 kg. She has a past medical history of type 2 diabetes, depression, epilepsy obesity and previously surgically treated breast cancer. She takes sitagliptin, gliclazide, topiramate, liraglutide and fluoxetine.

The examination is unremarkable other than an elevated body mass index of 35 kg/m^2.

What medication is responsible for her symptoms?

	Fluoxetine	10%
🟩	Gliclazide	74%
🟥	Liraglutide	5%
	Sitagliptin	6%
	Topiramate	5%

Sulfonylureas often cause weight gain

Important for me Less important

Gliclazide is correct. This medication can cause weight gain and so is best avoided in those patients with diabetes and obesity.

Fluoxetine is incorrect. This is associated with weight loss rather than weight gain. Mirtazapine is an antidepressant that causes weight gain.

Liraglutide is incorrect . This medication is typically associated with weight loss.

Sitagliptin is incorrect. This does not cause weight gain and so is a more suitable choice in patients who are overweight with type 2 diabetes.

Topiramate is incorrect. This medication used in the treatment of epilepsy causes weight loss.

Discuss Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

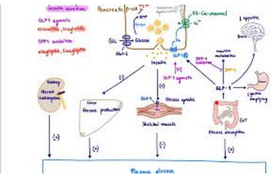
Next question

Textbooks

High-yield textbook

Extended textbook

Media



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

Report broken media

Score: **24%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗

PassMedicine

Question 126 of 414 ✓

An 18-year-old male is reviewed due to concerns about delayed pubertal development, despite being 1.77m tall. On examination he has scant pubic hair and reduced testicular volume. The following blood results are obtained:

Testosterone	6.7 nmol/l (9 - 30)
LH	3 .1 mu/l (3 - 10)
FSH	5.7 mu/l (3 - 10)

What is the most likely diagnosis?

Klinefelter's syndrome	49%
Acute lymphoblastic leukaemia	0%
Testicular feminisation syndrome	5%
Primary testicular failure	10%
[✓ Kallman's syndrome]	35%

Kallman's syndrome - LH & FSH low-normal and testosterone is low

Important for me Less important

The LH and FSH levels are inappropriately low-normal given the low testosterone concentration, which points towards a diagnosis of hypogonadotrophic hypogonadism. In Klinefelter's syndrome the LH and FSH levels are raised

Discuss (10) Improve

Next question

Kallmann's syndrome

Kallmann's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallmann's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty.

Features

- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above-average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Management

- testosterone supplementation
- gonadotrophin supplementation may result in sperm production if fertility is desired later in life

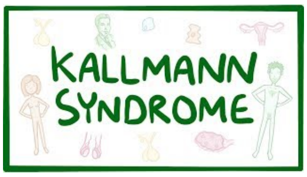
Next question

Textbooks

High-yield textbook

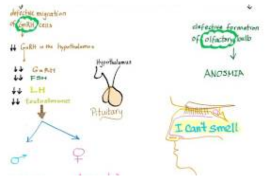
Extended textbook

Media


KALLMANN SYNDROME

Kallman's syndrome

Osmosis - YouTube 👍 42 👎 1


ANOSMIA
Hypothalamus
Pituitary
I can't smell

Kallmann Syndrome mnemonic

Medicosis Perfectionalis - YouTube 👍 7 👎 6

Report broken media

Score: **24.6%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗
16	✗
17	✓

A 42-year-old woman with known polycystic ovarian syndrome (PCOS) and coronary artery disease is seen in the clinic following a fasting glucose test confirming a new diagnosis of type 2 diabetes.

The patient is already established on metformin 500mg BD due to her PCOS and dietary changes have been unsuccessful in reducing her glucose recordings. Base level investigations confirm no renal or liver impairment.

What should be trialled prior to commencing an SGLT-2 inhibitor in this patient?

	A DPP 4 inhibitor	19%
🟩	A higher dose of metformin	67%
🟥	A sulfonylurea	10%
	A thiazolidinediones/glitazone	3%
	An alpha-glucosidase inhibitor	2%

If starting an SGLT-2 as initial therapy for T2DM then ensure metformin is titrated up first

Important for me Less important

This patient has a new diagnosis of type 2 diabetes and given her previous history of cardiovascular disease an SGLT-2 inhibitor would be a suitable anti-diabetic medication to commence. Although the patient is established on metformin, it should be titrated up to the maximum dose (1g BD) prior to commencing an SGLT-2 inhibitor. For this reason, a **higher dose of metformin** should be trialled. If tolerated this dose of metformin should be continued and an SGLT-2 inhibitor then added. If this higher dose results in unacceptable side effects a modified release form of the drug can be trialled or an SGLT-2 inhibitor started with the previous dose of metformin.

DPP 4 inhibitors can be used as an alternative second-line anti-diabetic medication to SGLT-2 inhibitors however they are not recommended in patients at risk of heart failure with studies indicating the drug can accelerate/increase the chance of the condition. DDP 4 and SGLT-2 inhibitors can be used in combination but one does not need to be used before the other.

Sulfonylureas have been associated with an increased risk of developing heart failure and therefore should be avoided if possible, in patients with cardiovascular disease. They can be used alongside SGLT-2 inhibitors if appropriate but do not need to be trialled prior to SGLT-2 inhibitor use.

Thiazolidinediones/glitazone, such as pioglitazone, are another alternative second-line treatment to SGLT-2 inhibitors or can be used as a third agent in addition to SGLT-2 inhibitors. Again these anti-diabetic drugs can cause fluid retention and therefore should be avoided in patients at risk of heart failure.

Alpha-glucosidase inhibitors are a separate group of drugs used in the management of diabetes that reduced the digestion of carbohydrates, therefore reducing a patient's glucose intake. They can be used with or without SGLT-2 inhibitors but do not have to be trialled prior to SGLT-2 inhibitor use.

👍 👎 Discuss (6) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

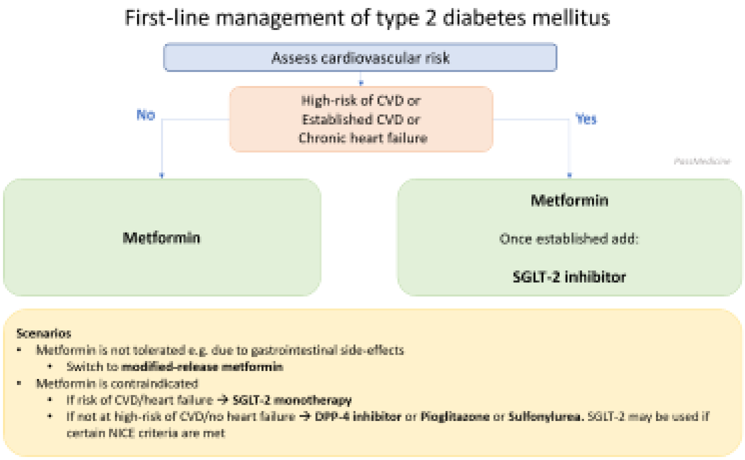
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor
Scenarios
Metformin is not tolerated e.g. due to gastrointestinal side-effects
Switch to modified-release metformin
Metformin is contraindicated
If risk of CVD/heart failure → SGLT-2 monotherapy
If not at high-risk of CVD/no heart failure → DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

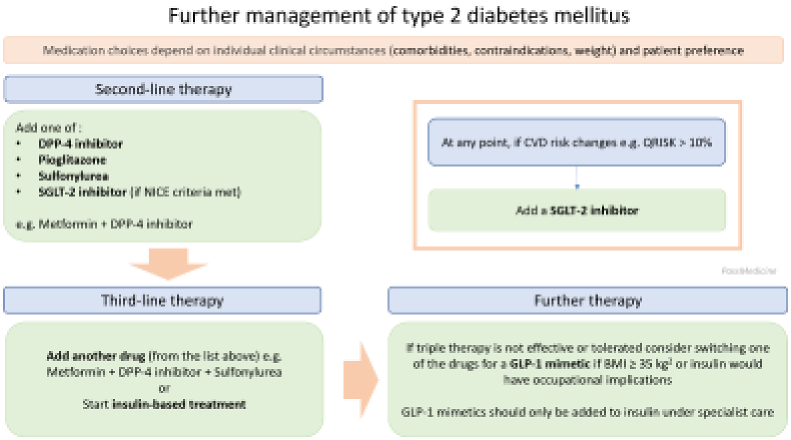
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

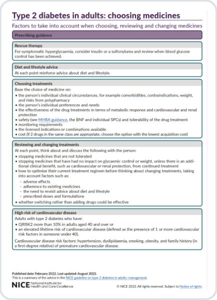
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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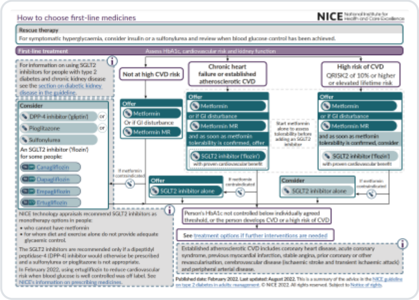

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR

Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated
Offer
SGLT2 inhibitor alone
If metformin contraindicated
Consider
SGLT2 inhibitor alone
If metformin contraindicated

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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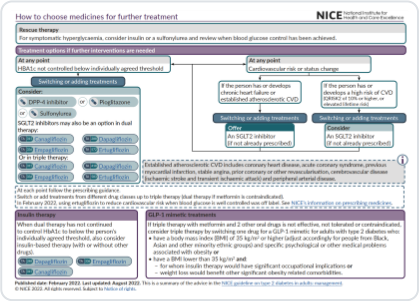

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments
Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Or in triple therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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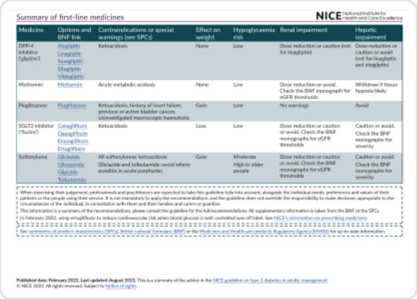

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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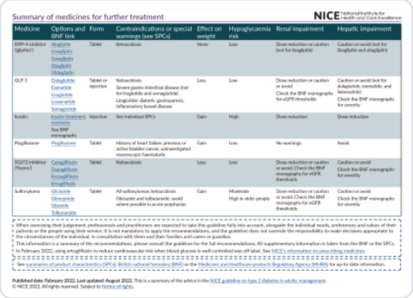

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

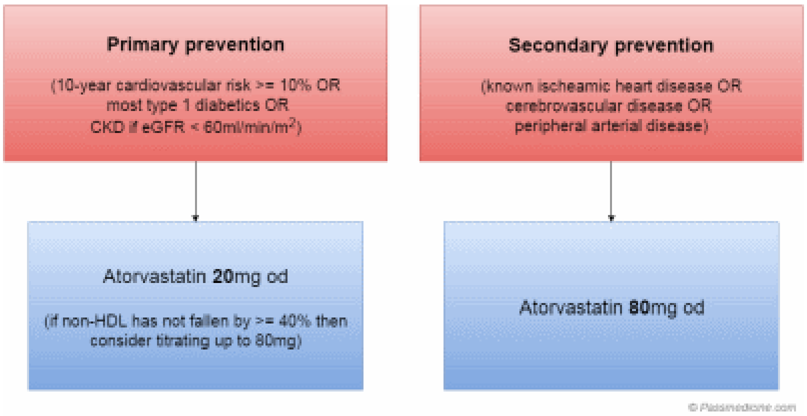
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

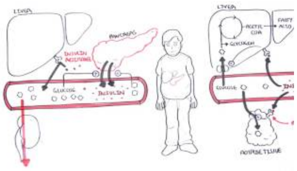
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media

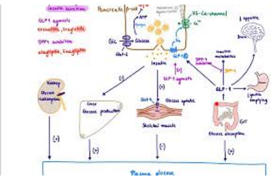


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

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Score: **24.4%**

1 ✓
2 ✓
3 ✓

PassMedicine

Question 128 of 414 ×

A 68-year-old woman has recently had blood tests arranged by her GP as part of her annual medication review. She has a history of hypothyroidism, type 2 diabetes, hypertension and osteopaenia. She takes levothyroxine, metformin, ramipril and calcium and vitamin D supplements.

Her blood tests show the following:

Thyroid-stimulating hormone (TSH)	7.8 mU/L	(0.5-5.5)
Free thyroxine (T4)	8.9 pmol/L	(9.0 - 18)

On further questioning, she reports that she normally takes her levothyroxine on an empty stomach at 8 am every morning, followed by her other regular medications at 8.30 am. She denies any recently missed doses.

What advice should be given regarding her medication timings in order to improve her thyroid status?

	Take levothyroxine with a glass of orange juice	2%
	Take levothyroxine with breakfast	4%
🟥	Take levothyroxine at least 1 hour before all other medications	21%
🟩	Take calcium supplement at least 4 hours after levothyroxine	70%
	Take metformin at least 4 hours after levothyroxine	4%

Iron / calcium carbonate tablets can reduce the absorption of levothyroxine - should be given 4 hours apart

Important for me Less important

This woman has borderline hypothyroid results from her blood tests, with a raised TSH and slightly low free T4. Before the decision to increase her levothyroxine dose is made, it is good practice to ensure that she is taking her current dose properly. While the standard advice is to take it at least 30 minutes before breakfast, caffeine-containing liquids or other medication, it is known that certain medications can directly reduce the absorption of levothyroxine and hence the spacing interval needs to be extended. Calcium carbonate is known to be one of these medications and the British National Formulary advises separate administration by at least 4 hours.

Taking levothyroxine with orange juice is incorrect, as this does not improve levothyroxine absorption. Orange juice is sometimes recommended to be taken alongside iron supplements, as vitamin C is known to promote iron absorption.

Taking levothyroxine with breakfast is incorrect as this would have the opposite effect and would likely reduce levothyroxine absorption further. Medications that should be taken with food include non-steroidal anti-inflammatory drugs.

Taking levothyroxine at least 1 hour before all other medications is good advice in general, but would not be the appropriate advice in cases where there is a known drug interaction (i.e. calcium supplements). Other drugs that require a minimum of 4-hour dose separation with levothyroxine include antacids and iron.

Taking metformin at least 4 hours after levothyroxine is incorrect as this would not have any noticeable benefit on levothyroxine absorption. Patients who are treated with levothyroxine may experience higher glucose levels and need adjustment of their antidiabetic drugs.

👍 👎 💬 Discuss (1) Improve

Next question

Hypothyroidism: levothyroxine therapy ★

Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value

- there is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions

- iron, calcium carbonate
    - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 7 👎 6

Management of hypothyroidism

Report broken link

Media

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Question 129 of 414 ✗

A 60-year-old woman presented to the emergency department following a seizure. Her husband witnessed the seizure and noted that all 4 of her limbs were jerking during the event and she that was incontinent of urine. Her seizures have terminated but she remains significantly confused.

He mentions that she had been recently diagnosed with lung cancer 6 weeks ago. Given her low mood following her diagnosis, she was started on an antidepressant. Since then, she has been feeling nauseous and fatigued but had put this down to her depression.

Her physical examination revealed moist mucous membranes. Her heart rate was 90 beats/minute and her blood pressure was 120/70mmHg.

Blood tests were performed and the results were:

Na^+	115 mmol/L	(135 - 145)
K^+	4.2 mmol/L	(3.5 - 5.0)
Urea	6.5 mmol/L	(2.0 - 7.0)
Creatinine	110 µmol/L	(55 - 120)
Calcium	2.35 mmol/L	(2.1-2.6)
Phosphate	1.0 mmol/L	(0.8-1.4)
Magnesium	0.85 mmol/L	(0.7-1.0)

Random cortisol	600nmol/L	>350nmol/L
Thyroid-stimulating hormone (TSH)	4.0 mU/L	(0.5-5.5)
Plasma osmolality	235 mOsm/kg	285-295
Urine osmolality	335mOsm/kg	50-1200 mOsm/kg
Urinary sodium	35 mOsm/kg	<20mOsm/kg

What treatment should be started given her symptoms?

0.9% sodium chloride solution	6%
[✓ Demeclocycline]	7%

Tolvaptan	6%
Strict 1L fluid restriction	22%
3% sodium chloride solution	59%

Hypertonic saline is usually indicated in patients with acute, severe, symptomatic hyponatraemia (< 120 mmol/L)

Important for me Less important

The diagnosis of lung cancer and the initiation of a new antidepressant should always raise the suspicion for underlying hyponatremia. The presence of seizures with this indicates that this is a severe case of hyponatremia. Looking at the remainder of her blood tests, the likely underlying cause is SIADH.

Hypertonic saline is normally the first-line treatment in severe hyponatremia and should be initiated in a high-dependency unit. Normally a bolus of 150mls of 3% sodium chloride is used with repeat blood tests performed 30 minutes after the first bolus. A 2nd bolus can be performed if an increase of 5mmol/L of sodium is not achieved.

0.9% sodium chloride is used after the boluses of 3% sodium chloride. The aim at this stage is to raise sodium levels by 10mmol/L over the first 24 hours and 8mmol/L for every 24 hours after that.

Fluid restriction should be initiated in the setting of mild hyponatremia but will not correct this severe hyponatremia sufficiently to prevent morbidity. 3% hypertonic saline would be more appropriate as this will provide the necessary correction more quickly.

Demeclocycline and tolvaptan tend to be used in the setting of chronic hyponatremia that is not correcting with fluid restriction and slow sodium tablets. Its use is normally not recommended in severe hyponatremia and is only initiated under the guidance of endocrinology.

👍 👎 Discuss (5) Improve

Next question

Hyponatraemia: treatment ★

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:

- duration of hyponatremia: is it acute or chronic?
    - acute: develops over a period of < 48 hours
    - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
    - mild: 130-134 mmol/L
    - moderate: 120-129 mmol/L
    - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
    - patients with mild hyponatraemia may be symptomatic
    - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
    - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
    - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
    - euvolemic hyponatraemia: SIADH
    - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected

- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
    - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
    - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider medications:
    - demeclocycline
    - vaptans (see below)

If a hypervolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):
- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)
- can occur due to over-correction of severe hyponatremia
- pathophysiology:
    - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
    - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination

  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

B *I* A T↕

Textbooks

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Extended textbook

Links

Royal College of Physicians 👍 15 👎 3

2017 Hyponatraemia â€“ presentations and management

Report broken link

Score: **24%**

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Question 130 of 414 ✗

A 23-year-old woman is diagnosed with Graves' disease. Which one of the following statements regarding treatment is correct?

🟩	Block-and-replace regimes are usually of a shorter duration than carbimazole titration therapy	38%
🟥	Concurrent administration of propranolol and carbimazole should be avoided	7%
	Patients on block-and-replace regimes have fewer side-effects than those using titration therapy	21%
	Carbimazole should be started at no higher than 10mg/day for patients commencing a titration regime	16%
	In the block-and-replace regime levothyroxine should be started at the same time as carbimazole	18%

Discuss (8) Improve

Next question

Graves' disease: management

Despite many trials, there is no clear guidance on the optimal management of Graves' disease. Treatment options include anti-thyroid drugs (ATDs, for example carbimazole), radioiodine treatment and surgery.

Anti-thyroid drugs have emerged as the most popular first-line therapy for Graves' disease in recent years. Factors that particularly support their use include anti-thyroid drugs significant symptoms of thyrotoxicosis, or patients with a significant risk of hyperthyroid complications (e.g. elderly patients, cardiovascular disease).

Initial treatment to control symptoms

- propranolol is used to help block the adrenergic effects

NICE Clinical Knowledge Summaries recommended that patients with Graves' disease are referred to secondary care for ongoing treatment.

- NICE suggest carbimazole should be considered in primary care if patients symptoms are not controlled with propanolol

ATD therapy

- carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- the major complication of carbimazole therapy is agranulocytosis
- an alternative regime is termed 'block-and-replace'
    - carbimazole is started at 40mg
    - thyroxine is added when the patient is euthyroid
    - treatment typically lasts for 6-9 months
    - patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime

Radioiodine treatment

- often used in patients who relapse following ATD therapy or are resistant to primary ATD treatment
- contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years. Thyroid eye disease is a relative contraindication, as it may worsen the condition
- the proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

Next question

Textbooks

High-yield textbook

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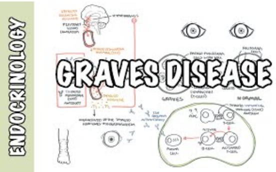
Links

Clinical Knowledge Summaries 👍 2 👎 1

Graves' disease: management

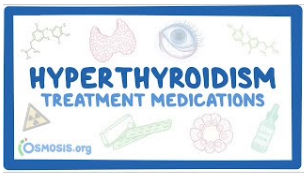
Report broken link

Media


ENDOCRINOLOGY
GRAVES DISEASE

Graves' disease

Armando Hasudungan - YouTube 👍 6 👎 0


HYPERTHYROIDISM
TREATMENT MEDICATIONS
OSMOSIS.org

Hyperthyroidism treatment medications

Osmosis - YouTube 👍 6 👎 1

Report broken media

Score: **23.8%**

1 ✓
2 ✓
3 ✓
4 ✗

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Question 131 of 414 ✕

An 80-year-old man is admitted with a 3 month history of gradual decline and dizziness on standing, followed by a 3 day history of inability to mobilise, general weakness and nausea. The medical consultant asks you to perform a short synacthen test which returns as normal. Which cause of adrenocortical insufficiency has not been excluded?

	Infiltration of the adrenal gland by amyloidosis	7%
🟩	Enlarging pituitary malignancy	61%
	Haemorrhage into the adrenal gland	9%
	Autoimmune adrenal failure	15%
🟥	Infiltration of the adrenal gland by tuberculosis	7%

A normal short synacthen test does not exclude adrenocortical insufficiency due to pituitary failure

Important for me Less important

The short Synacthen test is a method of excluding adrenal insufficiency. A baseline cortisol level is taken, IV synthetic ACTH is then administered and a second cortisol level is taken 30 minutes later. If the cortisol post ACTH rises to > 420 nmol/L at 30 minutes, the adrenal response to ACTH is adequate and Addison's disease (adrenal failure) can be excluded.

However, this excludes only primary adrenal failure and does not exclude cortisol deficiency secondary to failure of the pituitary to produce ACTH. The correct answer is therefore pituitary failure due to damage by an enlarging malignancy. The other answers all cause damage to the adrenal gland.

NICE CKS: Addison's disease
https://cks.nice.org.uk/addisons-disease

Discuss (4) Improve

Next question

Addison's disease: investigations ★

In a patient with suspected Addison's disease the definite investigation is an ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If an ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:

- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

Next question

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Royal College of Physicians 👍 6 👎 4

2017 Adrenal insufficiency â€" recognition and management

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Question 132 of 414 ✗

A 43-year-old man is admitted to hospital with pneumonia. His past medical history includes Addison's disease for which he takes hydrocortisone (20mg in the mornings and 10mg in the afternoon). What is the most appropriate action with respect to his steroid dose?

	Continue to take the same dose	5%
🟩	Double hydrocortisone to 40mg mornings and 20mg afternoon	84%
🟥	Halve hydrocortisone to 10mg mornings and 5mg afternoon	5%
	Continue to take the same dose + prescribe a proton pump inhibitor	4%
	Continue the same morning dose + stop the afternoon dose	1%

Patients on long-term steroids should have their doses doubled during intercurrent illness

Important for me Less important

The correct answer is to **double hydrocortisone to 40mg mornings and 20mg afternoon**. This is because patients with Addison's disease who are under stress, such as in the case of an acute illness like pneumonia, require an increased dose of glucocorticoids to compensate for their body's increased need. According to UK guidelines, during times of stress or illness, it is recommended that patients double their usual dose of hydrocortisone.

The option to **continue to take the same dose** is incorrect as it does not account for the increased cortisol requirements during acute illness. Continuing the same dose may result in an adrenal crisis due to insufficient cortisol levels.

The option to **halve hydrocortisone to 10mg mornings and 5mg afternoon** would be inappropriate as it would further decrease the patient's cortisol levels during a time when they need more. This could lead to severe complications related to adrenal insufficiency.

The option to **continue to take the same dose + prescribe a proton pump inhibitor** does not address the primary issue of insufficient cortisol levels during acute illness. While proton pump inhibitors can help reduce gastric acid production and prevent gastrointestinal issues, they do not replace the need for appropriate glucocorticoid dosing in this scenario.

Lastly, the option to **continue the same morning dose + stop the afternoon dose** would also be inappropriate as it would result in even lower cortisol levels than continuing with his regular dosing schedule. This could exacerbate his condition and increase his risk of developing an adrenal crisis.

👍 👎 Discuss (5) Improve

Next question

Corticosteroids ★

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	**Glucocorticoid activity, high mineralocorticoid activity,**	**Predominant glucocorticoid activity, low mineralocorticoid activity**	**Very high glucocorticoid activity, minimal mineralocorticoid activity**
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

The side effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects

- endocrine
  - impaired glucose regulation
  - increased appetite/weight gain
  - hirsutism
  - hyperlipidaemia

- Cushing's syndrome
  - moon face
  - buffalo hump
  - striae
- musculoskeletal
  - osteoporosis
  - proximal myopathy
  - avascular necrosis of the femoral head
- immunosuppression
  - increased susceptibility to severe infection
  - reactivation of tuberculosis
- psychiatric
  - insomnia
  - mania
  - depression
  - psychosis
- gastrointestinal
  - peptic ulceration
  - acute pancreatitis
- ophthalmic
  - glaucoma
  - cataracts
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects
- fluid retention
- hypertension

Selected points on the use of corticosteroids:
- patients on long-term steroids should have their doses doubled during intercurrent illness
- longer-term systemic corticosteroids suppress the natural production of endogenous steroids. They should therefore not be withdrawn abruptly, as this may precipitate an Addisonian crisis
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have:
  - received more than 40mg prednisolone daily for more than one week
  - received more than 3 weeks of treatment
  - recently received repeated courses

Next question

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← Question 133 of 414 ✓ ⚐ →

A 36-year-old female with a BMI of 34 kg/m^2 is reviewed after managing to lose 3 kg in the past month. She asks about the possibility of starting a drug to help her lose weight. What is the primary mode of action of orlistat?

Leptin antagonist	15%
Pancreatic lipase inhibitor	39%
Prevents intestinal absorption of low-density lipoproteins	28%
HMG-CoA reductase inhibitor	5%
Centrally-acting appetite suppressant	12%

Orlistat works by inhibiting gastric and pancreatic lipase to reduce the digestion of fat

Important for me Less important

The primary mode of action of orlistat is to inhibit pancreatic lipases, which in turn will decrease the absorption of lipids from the intestine

👍 👎 Discuss (3) Improve

Next question

Obesity: classification and therapeutic options ★

Classification

BMI = weight (kg) / height (m) squared

Description	**BMI range (kg/m^2)**
Underweight	< 18.49

Description	BMI range (kg/m^2)
Normal	18.5 - 25
Overweight	25 - 30
Obese class 1	30 - 35
Obese class 2	35 - 40
Obese class 3	> 40

Management

The management of obesity consists of a step-wise approach:

- conservative: diet, exercise
- medical
  - orlistat
  - liraglutide
- surgical

Orlistat is a pancreatic lipase inhibitor used in the management of obesity. Adverse effects include faecal urgency/incontinence and flatulence. A lower dose version is now available without prescription ('Alli'). NICE have defined criteria for the use of orlistat. It should only be prescribed as part of an overall plan for managing obesity in adults who have:

- BMI of 28 kg/m^2 or more with associated risk factors, or
- BMI of 30 kg/m^2 or more
- continued weight loss e.g. 5% at 3 months
- orlistat is normally used for < 1 year

Liraglutide

- a glucagon-like peptide-1 (GLP-1) mimetic that is used in the management of type 2 diabetes mellitus (T2DM)
- given as a once daily subcutaneous injection
- when used in the management of T2DM it was noted to cause weight loss in a significant proportion leading to research interest in its use in obesity
- current NICE criteria for use (see link for full criteria):
  - person has a BMI of at least 35 kg/m^2
  - prediabetic hyperglycaemia (e.g. HbA1c 42 - 47 mmol/mol)

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 6 👎 1

2020 Liraglutide for managing overweight and obesity

NICE 👍 2 👎 5

Obesity guidelines

Report broken link

Media

OBESITY
OVERVIEW

Approach to obesity and weight gain

Armando Hasudungan - YouTube 👍 4 👎 1

Report broken media

Score: **24.1%**

Question 134 of 414

An 84-year-old woman presents to her general practitioner with reports of needing to frequently rush to the bathroom to pass urine. Occasionally, she does not make it in time. She has a past medical history of hypertension. Her medications include amlodipine and ramipril.

On examination, there is no palpable bladder.

What is the most appropriate medication choice for this patient's symptoms?

🟩	Mirabegron	55%
	Oxybutynin	32%
	Solifenacin	4%
🟥	Tamsulosin	3%
	Tolterodine	6%

Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative

Important for me Less important

Mirabegron is correct. The patient has urge incontinence. Mirabegron is a beta3 agonist used in the treatment of urge incontinence. It has been shown to be equally as effective as anti-cholinergic medications in treating the symptoms of urge incontinence but without the anti-cholinergic side effects (i.e. these medications may precipitate confusion in the elderly).

Oxybutynin is incorrect. This is a medication used in the treatment of urge incontinence. It works by a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. However, it is a less suitable choice than mirabegron in a patient that is 84 years of age as its anticholinergic effects may precipitate confusion in the elderly.

Solifenacin is incorrect. Solifenacin is a competitive cholinergic receptor antagonist, which selects the M3 receptor subtype. This results in reduced bladder tone and allows the bladder to hold larger volumes. Again, this is a less suitable choice than mirabegron because its anticholinergic effects may precipitate confusion in the elderly.

Tamsulosin is incorrect. This is an alpha-antagonist used to treat benign prostatic hypertrophy rather than urge incontinence in women.

Tolterodine is incorrect. This acts at M2 and M3 muscarinic receptors and is another anticholinergic medication used in the treatment of urge incontinence. It is typically felt to have fewer side effects compared with older treatments like oxybutynin. However, the issue of anticholinergic side effects still remains and therefore mirabegron is still preferred in the elderly population.

👍 👎 Discuss (2) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
    - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
    - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
    - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
    - a combined noradrenaline and serotonin reuptake inhibitor
    - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

Report broken link

Media

URINARY INCONTINENCE

Urinary incontinence

Osmosis - YouTube 👍 0 👎 1

Report broken media

Score: **23.9%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓

PassMedicine

Question 135 of 414 ✗

A 4-year-old child is referred to the paediatric clinic with a suspected diagnosis of the rare renal disorder Bartter's syndrome having originally presented with failure to thrive and electrolyte imbalance on blood tests.

Further investigations confirm the diagnosis and the child is commenced on electrolyte supplementation and an ACE inhibitor following consultation with a paediatric renal specialist.

What aspect of the renal system is affected by this condition?

Calcium channel pumps	1%
Potassium channels	5%
🟥 Sodium, chloride channels	10%
Sodium, potassium, ATPase pump	18%
🟩 Sodium, potassium, chloride pumps	65%

Bartter's syndrome results from a defective NKCC2 channel in the ascending loop of Henle

Important for me Less important

Bartter syndrome is a rare congenital renal defect affecting the thick ascending limb of the loop of Henle. Patients typically present from around the age of 2 years onwards with symptoms of polyuria, polydipsia and dehydration. A defect of the **sodium, potassium, chloride pumps** within the ascending limb results in features in keeping with loop-diuretic use, increasing the loss of potassium, sodium and water in urine. Investigations will therefore typically identify hypokalaemia and alkalosis with normal to low blood pressure. Treatment includes monitoring and correcting electrolyte imbalance, spironolactone to reduce potassium loss and ACE inhibitors to reduce glomerular filtration rate.

Calcium channel pumps play a significant role in specific cell functions including cell signal transduction and muscle contraction. There are limited calcium-specific channels within the renal systems and they are not affected in Bartter's syndrome.

Potassium channels are most commonly involved in the repolarisation of neurons following sodium-induced depolarisation however they are also found in the distal convoluted tubules of the renal systems. Defects of these channels can occur in conditions such as EAST syndrome (epilepsy, ataxia, sensorineural deafness and salt-wasting tubulopathy) however they are not affected in Bartter's syndrome.

Sodium, chloride channels are predominately found within the renal distal convoluted tubules and play a significant role in the water concentration of urine output. These channels are not affected in Bartter's syndrome.

Sodium, potassium, ATPase pump are enzymes found within the cell members throughout the body and are mainly involved in maintaining osmotic equilibrium and member potential in cells. These pumps, which utilise energy via ATP, are unaffected in Bartter's syndrome.

👍 👎 Discuss Improve

Next question

Bartter's syndrome

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na^+ K^+ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

> Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features
- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 9 👎 3

2012 Renal tubular disorders review

Report broken link

Score: **23.7%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗
12 ✓
13 ✗

PassMedicine

Question 136 of 414 ✗

An infant is seen by paediatrics due to polyhydramnios during pregnancy. Subsequent genetic testing identifies a defect in the Na-K-2Cl transporter.

Which of the following is associated with this syndrome?

	Bradycardia	4%
🟥	Hypoaldosteronism	18%
	Hypocalciuria	13%
	Low prostaglandin E2	4%
🟩	Normotension	61%

Bartter's syndrome is associated with normotension

Important for me Less important

The correct answer is normotension. The diagnosis here is that of Bartter's syndrome, given the presenting symptoms and the confirmed defect in the Na-K-2Cl transporter. It is usually inherited in an autosomal recessive fashion. As loop diuretics work by inhibiting Na-K-2Cl Bartter's has a similar effect to furosemide, causing hypokalemia but without hypertension, unlike other endocrine causes of hypokalemia (Conn's, Liddle's and Cushing's syndromes) which cause hypertension.

Bradycardia is not known to be associated with Bartter's syndrome.

Hyperaldosteronism, rather than hypoaldosteronism, is associated with Bartter's syndrome. As well as elevated aldosterone levels, elevated renin levels are seen.

Hypercalciuria, rather than hypocalciuria, is seen. This predisposes infants to develop kidney stones.

Bartter's syndrome is associated with increased production of prostaglandin E2, rather than decreased.

Discuss (1) Improve

Next question

Bartter's syndrome ★

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na$^+$ K$^+$ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

> Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features
- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

Next question

Textbooks

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Extended textbook

PassMedicine

Question 137 of 414 ✗

A 61-year-old man is seen in the endocrine clinic following investigations for weight gain and lethargy. He has no relevant past medical history and does not take any regular medications.

The results of his investigations are displayed below:

Na^+	149 mmol/L	(135 - 145)
K^+	2.9 mmol/L	(3.5 - 5.0)
Bicarbonate	33 mmol/L	(22 - 29)
Urea	6.4 mmol/L	(2.0 - 7.0)
Creatinine	101 µmol/L	(55 - 120)

24 hour urinary cortisol	272mcg/24hrs	(3.5 - 45)

8 AM cortisol after administration of low dose dexamethasone	212nmol/L	(<50)
8 AM cortisol after administration of high dose dexamethasone	42nmol/L	(>50% reduction vs low dose)

Where is the most likely source of this man's abnormality?

Adrenals	32%
Hypothalamus	9%
Kidneys	2%
Lungs	3%
Pituitary	54%

In Cushing's disease, cortisol is not suppressed by low-dose dexamethasone but is suppressed by high-dose dexamethasone

Important for me Less important

This man has presented with Cushing's syndrome, as evidenced by his raised urinary cortisol level and metabolic abnormalities. To determine the cause of Cushing's syndrome, a dexamethasone suppression test must be performed. His lack of response to low-dose dexamethasone confirms Cushing's syndrome. His positive response to high-dose dexamethasone confirms that the abnormality is related to the pituitary (Cushing's disease). This is because excess adrenocorticotropic hormone (ACTH) production from the pituitaries can be inhibited by high doses of dexamethasone, however autonomous cortisol production from the adrenals will not be affected.

As mentioned, the fact that this patient is responsive to high-dose dexamethasone is evidence that the adrenal glands are not responsible for this man's Cushing's syndrome. This is because dexamethasone inhibits ACTH hormone but has no direct effect on the adrenals. This is therefore an incorrect answer.

Disorders of the hypothalamus are generally associated with hypopituitarism, rather than hyperpituitarism. Furthermore, the positive response to the high dose dexamethasone is specific for Cushing's disease.

The electrolyte abnormalities seen here are due to Cushing's syndrome rather than any renal impairment. Note that the kidneys have no role in cortisol production.

Ectopic ACTH production from the lung is a possible cause of Cushing's syndrome however as with adrenal pathologies, this is not responsive to high dose dexamethasone.

👍 👎 Discuss (7) Improve

Next question

Cushing's syndrome: investigations ★

This section will consider:

- the general lab findings consistent with Cushing's syndrome
- tests to confirm whether a patient indeed has Cushing's syndrome
- tests to find the underlying cause of Cushing's syndrome

It is useful to bear in mind the possible causes:

- iatrogenic: corticosteroid therapy
- ACTH-dependent causes
  - Cushing's disease (a pituitary adenoma → ACTH secretion)
  - ectopic ACTH secretion secondary to a malignancy

- ACTH-independent causes
    - adrenal adenoma

General findings consistent with Cushing's syndrome

A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance.

Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels.

Tests to confirm Cushing's syndrome

The three most commonly used tests are:

- overnight (low-dose) dexamethasone suppression test
    - this is the most sensitive test and is now used first-line to test for Cushing's syndrome
    - patients with Cushing's syndrome do not have their morning cortisol spike suppressed
- 24 hr urinary free cortisol
    - two measurements are required
- bedtime salivary cortisol
    - two measurements are required

Localisation tests

The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

High-dose dexamethasone suppression test

The high-dose dexamethasone suppression test may be used to localise the pathology resulting in Cushing's syndrome. This test may be interpreted as follows:

Cortisol	ACTH	Interpretation
Not suppressed	Suppressed	Cushing's syndrome due to other causes (e.g. adrenal adenomas)
Suppressed	Suppressed	Cushing's disease (i.e. pituitary adenoma → ACTH secretion)
Not suppressed	Not suppressed	Ectopic ACTH syndrome

Other tests

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic ACTH secretion.

An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's.

Next question

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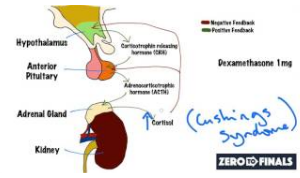
Media

CUSHING SYNDROME

Cushing syndrome

Osmosis - YouTube 👍 35 👎 2


Negative Feedback
Positive Feedback
Hypothalamus
Corticotrophin releasing hormone (CRH)
Dexamethasone 1mg
Anterior Pituitary
Adrenocorticotrophic hormone (ACTH)
Adrenal Gland
↑ Cortisol
(Cushings Syndrome)
Kidney
ZERO TO FINALS

PassMedicine

Question 138 of 414 ✗

A 33-year-old female is referred to endocrinology with thyrotoxicosis. Following a discussion of management options she elects to have radioiodine therapy. Which one of the following is the most likely adverse effect?

Hypothyroidism	39%
Thyroid malignancy	3%
Agranulocytosis	8%
Oesophagitis	3%
Precipitation of thyroid eye disease	47%

It is well documented that radioiodine therapy can precipitate thyroid eye disease but a majority of patients will eventually require thyroxine replacement

Discuss (5) Improve

Next question

Graves' disease: management

Despite many trials, there is no clear guidance on the optimal management of Graves' disease. Treatment options include anti-thyroid drugs (ATDs, for example carbimazole), radioiodine treatment and surgery.

Anti-thyroid drugs have emerged as the most popular first-line therapy for Graves' disease in recent years. Factors that particularly support their use include anti-thyroid drugs significant symptoms of thyrotoxicosis, or patients with a significant risk of hyperthyroid complications (e.g. elderly patients, cardiovascular disease).

Initial treatment to control symptoms

- propranolol is used to help block the adrenergic effects

NICE Clinical Knowledge Summaries recommended that patients with Graves' disease are referred to secondary care for ongoing treatment.

- NICE suggest carbimazole should be considered in primary care if patients symptoms are not controlled with propanolol

ATD therapy

- carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- the major complication of carbimazole therapy is agranulocytosis
- an alternative regime is termed 'block-and-replace'
    - carbimazole is started at 40mg
    - thyroxine is added when the patient is euthyroid
    - treatment typically lasts for 6-9 months
    - patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime

Radioiodine treatment

- often used in patients who relapse following ATD therapy or are resistant to primary ATD treatment
- contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years. Thyroid eye disease is a relative contraindication, as it may worsen the condition
- the proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

Next question

Textbooks

High-yield textbook

Extended textbook

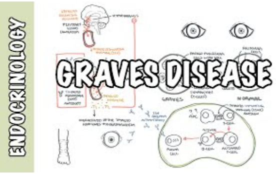
Links

Clinical Knowledge Summaries 👍 2 👎 1

Graves' disease: management

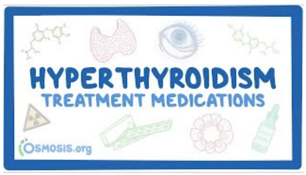
Report broken link

Media


ENDOCRINOLOGY
GRAVES DISEASE

Graves' disease

Armando Hasudungan - YouTube 👍 6 👎 0


HYPERTHYROIDISM
TREATMENT MEDICATIONS
OSMOSIS.org

Hyperthyroidism treatment medications

Osmosis - YouTube 👍 6 👎 1

Report broken media

Score: **23.2%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓

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Question 139 of 414 ✓

A 43-year-old man is admitted to the endocrine ward following a one-month history of polyuria and polydipsia. He appears severely dehydrated. A water deprivation test is performed which shows the following result.

Urine osmolality post-fluid deprivation	37mOsm/kg	(50-1200)
Urine osmolality post-desmopressin	45mOsm/kg	(50-1200)

What is the diagnosis?

Cranial diabetes insipidus	12%
Inconclusive result	3%
[✓ Nephrogenic diabetes insipidus]	76%
Primary polydipsia	4%
Syndrome of inappropriate ADH secretion (SIADH)	4%

Water deprivation test: nephrogenic DI

- urine osmolality after fluid deprivation: low
- urine osmolality after desmopressin: low

Important for me Less important

Nephrogenic diabetes insipidus (DI) is the correct answer. ADH is secreted by the hypothalamus and acts on renal tubules to increase fluid reabsorption. In nephrogenic DI, although there is ADH production by the hypothalamus, there is a failure of the kidneys to respond to the hormone. Accordingly, following fluid deprivation, there is a failure to concentrate urine due to the absence of a renal tubular response to ADH. Following administration of desmopressin, the urine remains dilute as, again, the kidneys do not respond to ADH.

Cranial diabetes insipidus is incorrect, although clinically it would present in the same way. In cranial diabetes insipidus, there is a failure of hypothalamic production of ADH. Accordingly, after fluid deprivation, urine is dilute due to a failure to reabsorb water from the urine in the absence of

ADH production. However, following desmopressin administration, the urine will become concentrated as the renal tubules are still responsive to ADH, hence reabsorption occurs.

An inconclusive result is not correct - as explained above, the result is diagnostic for nephrogenic diabetes insipidus.

Primary polydipsia is incorrect, although clinically it would present in the same way. In primary polydipsia excessive fluid intake occurs in the absence of a physiological stimulus to drink; there is adequate hypothalamic ADH production and an adequate renal tubular response to ADH. Therefore, following fluid deprivation the body is already able to effectively concentrate urine, and after desmopressin urine remains concentrated due to the presence of a renal tubular response to ADH.

SIADH is incorrect. SIADH is over-production of ADH in the absence of a physiological stimulus. Clinically this would not cause polydipsia and polyuria, and patients would be euvolaemic or hypervolaemic, often with hyponatraemia. A fluid deprivation test cannot diagnose SIADH; urine osmolality is likely to be high due to excessive reabsorption of water due to excessive ADH production. More important in the diagnosis of SIADH is a paired urine and serum osmolality and sodium.

Discuss Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

Textbooks

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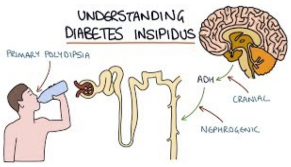
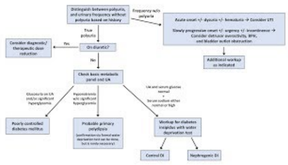
Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5



An Approach to Polyuria

Strong Medicine - YouTube 👍 29 👎 4

Report broken media

PassMedicine

Question 140 of 414 ✓

A 31-year-old female with polycystic ovarian syndrome consults you as she is troubled with excessive facial hair. Switching her combined oral contraceptive pill to co-cyprindiol has had no effect. On examination she has hirsutism affecting her moustache, beard, and temple areas. What is the most appropriate treatment?

Topical salicylic acid	2%
Topical adapalene	5%
Oral clomifene	26%
Topical eflornithine	63%
Topical tazarotene	4%

The most appropriate treatment for this patient with excessive facial hair due to polycystic ovarian syndrome is **topical eflornithine**. Eflornithine is a topical cream that works by inhibiting ornithine decarboxylase, an enzyme required for hair growth. It has been shown to be effective in reducing the growth of unwanted facial hair in women, particularly when other treatments such as combined oral contraceptive pills have failed.

Topical salicylic acid is not an appropriate treatment for hirsutism. Salicylic acid is commonly used as a keratolytic agent in the management of acne and warts. It works by causing the cells of the epidermis to shed more readily, which can help clear pores and reduce inflammation. However, it does not have any effect on hair growth or the hormonal imbalances that contribute to hirsutism.

Similarly, **topical adapalene** and **topical tazarotene** are also not suitable treatments for hirsutism. Both of these agents are retinoids that are primarily used in the management of acne vulgaris due to their ability to modulate keratinocyte differentiation and reduce inflammation. They do not affect hair growth or address the underlying hormonal causes of hirsutism.

Finally, **oral clomifene** is not indicated for the treatment of hirsutism either. Clomifene is a selective estrogen receptor modulator (SERM) that is used to induce ovulation in women with anovulatory infertility related to conditions such as polycystic ovarian syndrome. While it may improve fertility outcomes in some patients with PCOS, it does not specifically target hair growth or other symptoms related to hyperandrogenism like hirsutism.

Discuss (5) Improve

Next question

Polycystic ovarian syndrome: management

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

General
- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne
- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility
- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

Next question

Textbooks

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Extended textbook

Links

RCOG 👍 4 👎 0

Opinion paper on metformin in PCOS

ESHRE (European Society of Human Reproduction and Embryology) 👍 1 👎 0

2018 International Evidence Based Guideline for the Assessment and Management of PCOS

Patient.info 👍 1 👎 0

Polycystic ovarian syndrome review

Clinical Knowledge Summaries 👍 3 👎 1

Polycystic ovarian syndrome

Royal College of Obstetricians and Gynaecologists 👍 2 👎 1

2014 Long-term Consequences of Polycystic Ovary Syndrome

PassMedicine

← Question 141 of 414 ✗ ⚐ →

A 43-year-old woman is referred to the endocrine clinic with symptoms of weight gain, fatigue and headache. She was also recently diagnosed with type two diabetes.

On examination, you note truncal obesity with proximal wasting of the arms and legs. Hirsutism is present, and the skin appears thin with multiple striae and bruises.

You suspect Cushing's syndrome and perform routine blood tests as part of your investigations.

What biochemical abnormality would you expect to find in this condition?

	Hypercalcaemia	1%
	Hyperkalaemic metabolic acidosis	8%
🟥	Hyperkalaemic metabolic alkalosis	9%
	Hypokalaemic metabolic acidosis	14%
🟩	Hypokalaemic metabolic alkalosis	69%

Cushing's syndrome - hypokalaemic metabolic alkalosis

Important for me Less important

This patient has presented with several characteristic features of Cushing's syndrome.

In terms of biochemical abnormalities seen on routine testing, Cushing's syndrome often results in impaired glucose tolerance and hyperglycaemia, as seen in this patient. A hypokalaemic metabolic alkalosis can also be seen, as a result of increased renal mineralocorticoid action from the excess cortisol. This results in an increased exchange of sodium and water for potassium and H+, leading to a hypokalaemic metabolic alkalosis.

This picture is also seen in Conn's syndrome.

Hypercalcaemia is not usually associated with Cushing's syndrome.

👍 | 👎 | 💬 Discuss (4) | Improve

Next question

Cushing's syndrome: investigations ★

This section will consider:
- the general lab findings consistent with Cushing's syndrome
- tests to confirm whether a patient indeed has Cushing's syndrome
- tests to find the underlying cause of Cushing's syndrome

It is useful to bear in mind the possible causes:
- iatrogenic: corticosteroid therapy
- ACTH-dependent causes
  - Cushing's disease (a pituitary adenoma → ACTH secretion)
  - ectopic ACTH secretion secondary to a malignancy
- ACTH-independent causes
  - adrenal adenoma

General findings consistent with Cushing's syndrome

A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance.

Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels.

Tests to confirm Cushing's syndrome

The three most commonly used tests are:
- overnight (low-dose) dexamethasone suppression test
  - this is the most sensitive test and is now used first-line to test for Cushing's syndrome
  - patients with Cushing's syndrome do not have their morning cortisol spike suppressed
- 24 hr urinary free cortisol
  - two measurements are required
- bedtime salivary cortisol
  - two measurements are required

Localisation tests

The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

High-dose dexamethasone suppression test

The high-dose dexamethasone suppression test may be used to localise the pathology resulting in Cushing's syndrome. This test may be interpreted as follows:

Cortisol	ACTH	Interpretation
Not suppressed	Suppressed	Cushing's syndrome due to other causes (e.g. adrenal adenomas)
Suppressed	Suppressed	Cushing's disease (i.e. pituitary adenoma → ACTH secretion)
Not suppressed	Not suppressed	Ectopic ACTH syndrome

Other tests

CRH stimulation
- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic ACTH secretion.

An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's.

Next question

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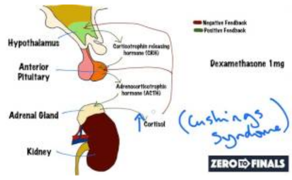
CUSHING SYNDROME

Cushing syndrome

Osmosis - YouTube 👍 35 👎 2


Negative Feedback
Positive Feedback
Hypothalamus
Corticotrophin releasing hormone (CRH)
Anterior Pituitary
Dexamethasone 1mg
Adrenocorticotrophic hormone (ACTH)
Adrenal Gland
↑Cortisol
(Cushings syndrome)
Kidney
ZERO TO FINALS

Understanding The Dexamethasone Suppression Test

Zero to Finals - YouTube 👍 118 👎 8

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Score: **24.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓

PassMedicine

Question 142 of 414 ✓

A 33-year-old woman presents to the diabetes outpatient clinic. She is 23 weeks pregnant with her first pregnancy. The patient did not have any medical conditions, including diabetes, before her pregnancy.

The patient was found to have gestational diabetes four weeks ago. She failed to respond to a two-week trial of diet and exercise and was started on metformin 500mg twice daily. She has been taking metformin for two weeks with excellent compliance.

An oral glucose tolerance test is performed.

Fasting blood glucose	6.3 mmol/L
Blood glucose two hours after oral glucose	6.9 mmol/L

What is the correct action?

Add second oral hypoglycaemic agent	2%
Continue with metformin and reassess in two weeks	28%
Increase dose of metformin	14%
[✓ Start insulin]	53%
Switch metformin to modified release preparation	4%

In gestational diabetes, if blood glucose targets are not met with diet/metformin then insulin should be added

Important for me Less important

Start insulin is the correct answer. In gestational diabetes, failure of a two-week trial of metformin warrants starting insulin. The target for fasting blood glucose in gestational diabetes is <5.3 mmol/L. The target for blood glucose two hours after an oral glucose tolerance test is <6.4 mmol/L. Therefore this patient's glycaemic control is insufficient on metformin alone.

Add second oral hypoglycaemic agent is the incorrect answer. Metformin is the only oral hypoglycaemic agent licenced for use in gestational diabetes. When gestational diabetes is not controlled with metformin, insulin should be started.

Continue with metformin and re-assess in two weeks is the incorrect answer. If gestational diabetes is not controlled after a two-week trial of metformin, insulin should be started. Delaying insulin initiation by two weeks increases the risk of complications.

Increase dose of metformin is the incorrect answer. Although there is scope to increase the dose of metformin, failure of glycaemic control following a two-week trial of metformin warrants initiation of insulin.

Switch metformin to modified-release preparation is the incorrect answer. Modified-release metformin is often considered when patients report side effects from metformin. There is no indication for modified-release metformin in this scenario. If gestational diabetes is not controlled after a two-week trial of metformin, insulin should be started.

👍 👎 Discuss (2) Improve

Next question

Gestational diabetes

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:
- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes
- BMI of > 30 kg/m^2
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes

- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
  - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
  - if glucose targets are still not met insulin should be added to diet/exercise/metformin
  - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Postgraduate Medical Journal DKA in pregnancy	👍 2 👎 2
NICE 2015 Management of diabetes in pregnancy	👍 3 👎 5

Report broken link

Media

PassMedicine

← Question 143 of 414 ✗ →

A 45-year-old lady was discharged from hospital following treatment with pamidronate for hypercalcaemia. She now presents with symptoms consistent of hypocalcaemia including muscle spasms and tetany. Which ECG changes are most likely to be present?

	T wave inversion	3%
	Peaked T waves	1%
🟩	Corrected QT interval prolongation	79%
🟥	U waves	6%
	Corrected QT interval shortening	12%

The clinical picture presented is not atypical when a patient who initially has hypercalcaemia is treated with bisphosphonates and rapidly develops hypocalcaemia.

The following ECG changes are associated with hypocalcaemia:

- Common: Corrected QT interval prolongation
- Rare: Atrial fibrillation or torsade de pointes

(Note: In hypercalcaemia shortening of the QT interval may be observed, in severe cases Osborn (or J-waves) may be present)/

Source: http://journal.publications.chestnet.org/article.aspx?articleid=1079481)

Discuss (2) Improve

Next question

Hypocalcaemia: features ★

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features

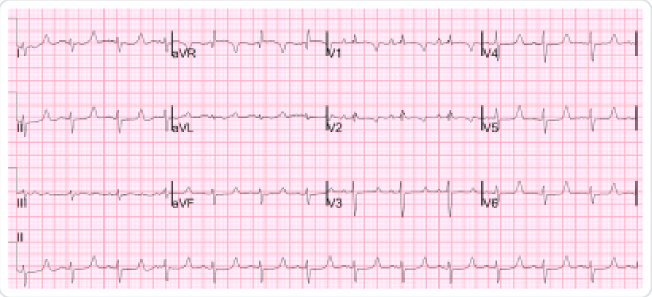
- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Trousseau's sign

- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers are drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people



Next question

Textbooks

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← Question 144 of 414 ✗ ⚐ →

An elderly woman, with multiple established medical issues, is referred to the endocrine clinic with symptoms of polydipsia, polyuria and general myalgia.

Serum blood tests confirm a raised calcium and parathyroid hormone level with imagining confirming the presence of a parathyroid adenoma.

Given the patient's presentation and other extensive comorbidities, conservative management instead of surgery was suggested. The patient agrees and is commenced on a calcimimetic medication.

On repeat blood tests a reduction in both calcium and PTH is seen and her symptoms improved.

What medication was the patient most likely commenced on?

	Alendronate	10%
🟥	Calcitonin	12%
	Calcitriol	4%
	Calcium carbonate	1%
🟩	Cinacalcet	73%

Cinacalcet is a calcimimetic - a drug that 'mimics' the action of calcium on tissue by allosteric activation of the calcium-sensing receptor

Important for me Less important

This patient has presented with the classical features of primary hyperparathyroidism with symptoms secondary to raised calcium, confirmed on blood tests and a raised parathyroid hormone (PTH) level. The definitive treatment for primary hyperparathyroidism is a total parathyroidectomy however conservative management may be used if specific severity markers are absent or if the patient is not fit for surgery (as in this patient). For these cases the medication **cinacalcet** maybe used. This is a calcimimetic drug that mimics the action of calcium on tissues including the parathyroid gland. It increases the sensitivity of calcium receptors on parathyroid cells, reducing PTH levels and resulting in a decrease in serum calcium levels.

Alendronate is a bisphosphonate used in the management of bone conditions including osteoporosis and Paget's disease. It works by inhibiting osteoclast-mediated bone resorption and therefore reduced bone breakdown but has no role in the management of hyperparathyroidism.

Calcitonin is a hormone secreted by the parafollicular cells of the thyroid gland. It acts to reduce blood calcium levels. Calcitonin is functionally an antagonist to PTH, and so is not a calcimimetic. Although it can be used for the treatment of hypercalcaemia it is not commonly used in the management of hyperparathyroidism.

Calcitriol, also known as 1,25-dihydroxycholecalciferol is the active form of vitamin D, normally produced in the kidney. Calcitriol results in an increased uptake of calcium from the intestines and therefore increases serum calcium level. As such it is used in the management of conditions resulting in hypocalcaemia including hypoparathyroidism and osteomalacia.

Calcium carbonate is mainly used therapeutically as a dietary calcium supplement and as a gastric antacid. It may also be used as a phosphate binder in conditions causing hyperphosphataemia such as renal impairment but again it has no role in the management of hyperparathyroidism.

👍 👎 Discuss Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':

- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations

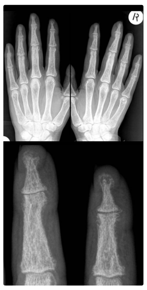
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- bloods
    - raised calcium, low phosphate
    - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
    - pepperpot skull
    - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



Next question

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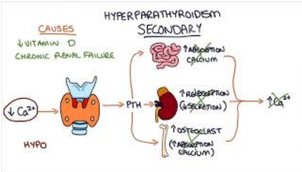
HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
HYPO
PTH
↑ABSORPTION CALCIUM
↑REABSORPTION (↓SECRETION)
↑OSTEOCLAST (↑ABSORPTION CALCIUM)
↑Ca2+

Understanding Hyperparathyroidism

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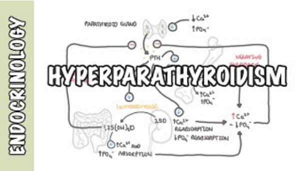
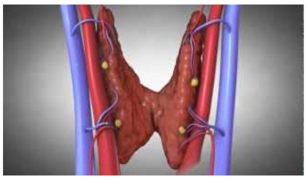

ENDOCRINOLOGY
HYPERPARATHYROIDISM
PARATHYROID GLAND
PTH

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2



Parathyroid Glands and Hyperparathyroidism

Norman Parathyroid Center - YouTube 👍 20 👎 5

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PassMedicine

← Question 145 of 414 ✓ →

Which one of the following unwanted effects is most likely to occur in patients taking gliclazide?

Peripheral neuropathy	2%
Cholestasis	4%
Photosensitivity	2%
Syndrome of inappropriate ADH secretion	9%
Weight gain	83%

All of the above side-effects may be seen in patients taking sulfonylureas but weight gain is the most common.

Discuss (1) Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects
- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects
- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression

- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

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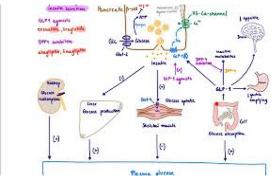

Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 34 10

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 12 5

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Question 146 of 414 ✗

Each one of the following is an acute phase protein, except:

	Haptoglobin	16%
	Alpha-1 antitrypsin	44%
🟥	CRP	3%
	Ferritin	6%
🟩	ESR	32%

The correct answer is **ESR**. ESR, or erythrocyte sedimentation rate, is not a protein but rather a test that indirectly measures how much inflammation is in the body. It does this by measuring the rate at which red blood cells settle in a test tube over one hour. The faster the red blood cells fall, the more likely it is there are high levels of inflammation.

Now let's discuss why the other options are incorrect.

Haptoglobin is indeed an acute phase protein. Its primary function is to bind free haemoglobin released from erythrocytes and thereby prevent iron loss and kidney damage. Levels of haptoglobin rise during inflammation, infection or after tissue injury.

Alpha-1 antitrypsin also falls into the category of acute phase proteins. It's primarily produced in the liver and its main function is to inhibit neutrophil elastase enzyme, preventing tissue damage especially in the lungs. Its level rises significantly during acute inflammatory responses.

CRP, or C-reactive protein, is another well-known acute phase protein. It's produced by the liver in response to factors released by macrophages and fat cells (adipocytes). CRP levels increase rapidly during inflammatory processes and can be used clinically as a marker for infection or inflammation.

Finally, **Ferritin** too belongs to the acute phase proteins group. Although it's primarily known as an intracellular storage site for iron, serum ferritin levels also rise dramatically in response to systemic inflammation or infection.

Discuss (4) Improve

Next question

Acute phase proteins

Acute phase proteins
- CRP*
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component**
- haptoglobin
- complement

During the acute phase response the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include:
- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

*Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesised in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

**plays a more significant role in other mammals such as mice

Next question

PassMedicine

Question 147 of 414 ✗

A 45-year-old man attends the clinic as he has developed swelling of both breasts. A systematic enquiry was otherwise unremarkable. He has a past medical history of heart failure for which he takes bisoprolol, furosemide, digoxin, amiodarone, and ramipril.

What is the most likely cause?

Amiodarone	21%
Bisoprolol	3%
🟩 Digoxin	64%
🟥 Furosemide	8%
Ramipril	4%

Digoxin can cause drug-induced gynaecomastia

Important for me Less important

Digoxin is correct. Digoxin is a well known cause of gynaecomastia. Digoxin is a cardiac glycoside that increases the force of myocardial contraction and reduces conductivity within the atrioventricular (AV) node. Indications for digoxin include rate control of atrial fibrillation or flutter and management of heart failure due to its positive inotropic effect. Other side effects include arrhythmias, nausea and vision disorders.

Amiodarone is incorrect. Gynaecomastia is not a known side effect of amiodarone. Side effects of amiodarone include arrhythmias, liver fibrosis, hyperthyroidism and cutaneous manifestations.

Bisoprolol is incorrect. Gynaecomastia is not a known side effect of bisoprolol. Side effects of bisoprolol include bradycardia, confusion, diarrhoea, dry eyes, and sleep disorders.

Furosemide is incorrect. Whilst this diuretic does not cause gynaecomastia, spironolactone is a well known cause. Side effects of furosemide include dizziness, hypokalemia, hyponatraemia, metabolic alkalosis and muscle spasms.

Ramipril is incorrect. Gynaecomastia is not a known side effect of ramipril. Side effects of ramipril include alopecia, angioedema, cough, hypotension, and renal impairment.

Discuss (1) Improve

Next question

Gynaecomastia

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan

PassMedicine

Question 148 of 414 ✕

A 38-year-old male with clinically suspected acromegaly has returned to the endocrine clinic for the results of investigations carried out last week. His blood tests confirm a raised insulin-like growth factor 1 (IGF-1).

What is the most appropriate next course of action?

	Confirm the diagnosis with an MRI pituitary	25%
	Random serum growth hormone (GH) level	2%
	Serum growth hormone-releasing hormone (GHRH) level	4%
🟩	Oral glucose tolerance test (OGTT) and serial growth hormone (GH) levels	59%
🟥	Start the patient on octreotide	11%

In the investigation of acromegaly, if a patient is shown to have raised IGF-1 levels, an oral glucose tolerance test (OGTT) with serial GH measurements is suggested to confirm the diagnosis

Important for me Less important

The Endocrine Society recommends that in patients with clinically suspected acromegaly, and an elevated or equivocal serum IGF-1 level, the diagnosis should be confirmed by finding a lack of GH suppression with an OGTT.

Carrying out a pituitary MRI may demonstrate a pituitary tumour. However, this is not the recommended investigation to confirm a diagnosis of acromegaly.

Confirming the diagnosis with a single GH level is incorrect as GH levels vary throughout the day and therefore cannot be used to confirm acromegaly.

Carrying out a GHRH level is not the next most appropriate investigation to confirm the diagnosis as the vast majority of acromegaly cases are due to pituitary adenomas. Acromegaly secondary to GHRH secreting tumours are rare and should only be investigated for cases where a pituitary defect cannot be confirmed.

Starting the patient on treatment for acromegaly is not the correct next course of action as the diagnosis must first be confirmed.

Discuss (3) Improve

Next question

Acromegaly: investigations

Growth hormone (GH) levels vary during the day and are therefore not diagnostic.

Serum IGF-1 levels have now overtaken the oral glucose tolerance test (OGTT) with serial GH measurements as the first-line test. The OGTT test is recommended to confirm the diagnosis if IGF-1 levels are raised.

The Endocrine Society guidelines suggest the following:

> *1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features.*
> ...
> *1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 µg/L following documented hyperglycemia during an oral glucose load.*

Serum IGF-1 may also be used to monitor disease

Oral glucose tolerance test
- in normal patients GH is suppressed to < 2 mu/L with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

The Endocrine Society 👍 8 👎 0

2014 Acromegaly guidelines

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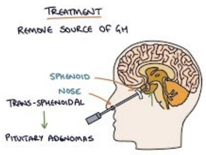
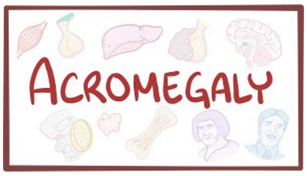
Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 12 👎 1


ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 6 👎 1

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Question 149 of 414 ✗

Each one of the following is a feature of pseudohypoparathyroidism, except:

	Short fourth and fifth metacarpals	9%
	Round face	19%
🟩	Normal calcium and phosphate levels	56%
	Cognitive impairment	11%
🟥	Short stature	4%

Discuss (3) Improve

Next question

Pseudohypoparathyroidism ★

Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in a G-protein. In type I pseudohypoparathyroidism there is a complete receptor defect whereas in type II the cell receptor is intact. Pseudohypoparathyroidism is typically inherited in an autosomal dominant fashion.

Bloods

- ↑ PTH
- ↓ calcium
- ↑ phosphate

Features

- short fourth and fifth metacarpals
- short stature
- learning difficulties

- obesity
- round face

Investigation

- an infusion of PTH followed by measurement of urinary phosphate and cAMP measurement - this can help differentiate between type I (neither phosphate or cAMP levels rise) and II (cAMP rises but phosphate levels do not change)

Next question

Textbooks

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Score: **24.2%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗

PassMedicine

Question 150 of 414 ✗

A 46-year-old female patient is admitted with a 3-month history of increasing fatigue and facial plethora. She has had heavy periods since 20 years of age, but this has improved since last year when she had a hormonal (progesterone) intrauterine device fitted.

She has a past medical history of exercise-induced asthma but rarely requires her salbutamol inhaler.

Her observations are broadly normal except for her blood pressure which is 150/95mmHg.

Routine blood tests show the following:

Haemoglobin	180	115-160 $*10^9$/L
White cell count	7.2	4-11 $*10^9$/L
Platelets	261	150-400 $*10^9$/L
Mean corpuscular volume	86	82-100 fl
Haematocrit	0.58	0.37-0.47 L/L

Which of the following would best explain this patient's presentation and blood results?

Asthma induced	4%
Dehydration	4%
Essential thrombocythemia	8%
Uterine fibroids	56%
JAK2 mutation	29%

Uterine fibroids may rarely be associated with secondary polycythaemia due to autonomous production of erythropoietin

Important for me Less important

This question provides a limited clinical history with some symptomatic and biochemical evidence of polycythaemia - a condition with many possible secondary causes.

Uterine fibroids are recognised to secret erythropoietin leading to polycythaemia, although this is rarely a clinical issue due to an association with dysfunctional uterine bleeding. In this case, the hormonal intrauterine device (Mirena coil) has successfully reduced the previous menorrhagia and uncovered this lesser-known clinical presentation of fibroids.

Polycythaemia can be secondary to chronic hypoxia. This may be commonly due to altitude-related physiological changes and chronic obstructive pulmonary disease (COPD) but it is not generally associated with asthma as asthma is a reversible obstructive airways disease.

Dehydration is a common cause of a biochemical picture consistent with polycythemia. However, in this case, the normal white cell and platelet counts, and lack of suggestive clinical history would point away from this diagnosis.

JAK2 mutation is associated with several haematological disorders but most strongly with polycythaemia rubra vera. This is more common in older age and associated with other blood and examination changes including thrombocythemia, neutrophilia, and hepatosplenomegaly. These are included in the World Health Organisation's diagnostic criteria. These criteria aren't eluded to in this scenario and this patients age and sex a diagnosis of uterine fibroids much more likely than a JAK2 mutation.

👍 👎 Discuss (7) Improve

Next question

Uterine fibroids

Fibroids are benign smooth muscle tumours of the uterus. They are thought to occur in around 20% of white and around 50% of black women in the later reproductive years.

Associations
- more common in Afro-Caribbean women
- rare before puberty, develop in response to oestrogen

Features
- may be asymptomatic
- menorrhagia
  - may result in iron-deficiency anaemia

- bulk-related symptoms
  - lower abdominal pain: cramping pains, often during menstruation
  - bloating
  - urinary symptoms, e.g. frequency, may occur with larger fibroids
- subfertility
- rare features:
  - polycythaemia secondary to autonomous production of erythropoietin

Diagnosis
- transvaginal ultrasound

Management

Asymptomatic fibroids
- no treatment is needed other than periodic review to monitor size and growth

Management of menorrhagia secondary to fibroids
- levonorgestrel intrauterine system (LNG-IUS)
  - useful if the woman also requires contraception
  - cannot be used if there is distortion of the uterine cavity
- NSAIDs e.g. mefenamic acid
- tranexamic acid
- combined oral contraceptive pill
- oral progestogen
- injectable progestogen

Treatment to shrink/remove fibroids
- medical
  - GnRH agonists may reduce the size of the fibroid but are typically used more for short-term treatment due to side-effects such as menopausal symptoms (hot flushes, vaginal dryness) and loss of bone mineral density
  - ulipristal acetate has been in the past but not currently due to concerns about rare but serious liver toxicity
- surgical
  - myomectomy: this may be performed abdominally, laparoscopically or hysteroscopically
  - hysteroscopic endometrial ablation
  - hysterectomy
- uterine artery embolization

Prognosis and complications

Fibroids generally regress after the menopause.

Some of the complications such as subfertility and iron-deficiency anaemia have been mentioned previously.

Other complications

- red degeneration - haemorrhage into tumour - commonly occurs during pregnancy

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 0 👎 0

Fibroids guidelines

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Media

UTERINE FIBROID
OSMOSIS.org

Uterine fibroids

Osmosis - YouTube

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← Question 151 of 414 ✗ ⚑ →

A 33-year-old Afro-Caribbean woman presents with a 6-month history of intermittent crampy abdominal pain and bloating. She also reports some mild constipation. She denies any vomiting or urinary symptoms.

Her past medical history includes appendicectomy and hypertension. She currently takes amlodipine 5mg once a day and drinks 8 units of alcohol per week.

On examination, her abdomen is soft with normal bowel sounds and there is a palpable firm non-tender abdominal mass arising from the pelvis.

Blood tests show:

Hb	179 g/L	Male: (135-180) Female: (115 - 160)
MCV	85 /fL	(80 - 100)
Platelets	153 * 10^9/L	(150 - 400)
WBC	8.3 * 10^9/L	(4.0 - 11.0)

Urea	4.3 mmol/L	(2.0 - 7.0)
Creatinine	82 μmol/L	(55 - 120)
Beta-hCG	5 mIU/mL	(<10)

What is the cause of the abnormal blood results?

🟩	Autonomous erythropoietin production due to uterine fibroid	71%
	Autonomous erythropoietin production due to ovarian cyst	9%
🟥	Excessive bone marrow red cell production due to a paraneoplastic syndrome	11%
	Excessive bone marrow red cell production due to polycythaemia vera	6%
	Physiological increase in marrow red cell production due to pregnancy	3%

Uterine fibroids may rarely be associated with secondary polycythaemia due to autonomous production of erythropoietin

Important for me Less important

This patient has uterine fibroids indicated by the symptoms and finding of a non-tender mass arising from the pelvis. Although rare, fibroids can autonomously secrete erythropoietin and result in secondary polycythaemia.

While ovarian cysts can cause all of her symptoms, ectopic erythropoietin secretion is not a recognised associated phenomenon.

A paraneoplastic syndrome would not normally give isolated polycythaemia.

Pregnancy is unlikely given the examination findings and is not supported by the low beta-hCG.

Polycythaemia vera is possible however is less likely given the young age of the patient and the lack of other symptoms. Furthermore there is clear indication of uterine fibroids in this patient.

👍 👎 Discuss (5) Improve

Next question

Uterine fibroids

Fibroids are benign smooth muscle tumours of the uterus. They are thought to occur in around 20% of white and around 50% of black women in the later reproductive years.

Associations
- more common in Afro-Caribbean women
- rare before puberty, develop in response to oestrogen

Features
- may be asymptomatic
- menorrhagia
  - may result in iron-deficiency anaemia
- bulk-related symptoms
  - lower abdominal pain: cramping pains, often during menstruation
  - bloating
  - urinary symptoms, e.g. frequency, may occur with larger fibroids

- subfertility
- rare features:
    - polycythaemia secondary to autonomous production of erythropoietin

Diagnosis

- transvaginal ultrasound

Management

Asymptomatic fibroids

- no treatment is needed other than periodic review to monitor size and growth

Management of menorrhagia secondary to fibroids

- levonorgestrel intrauterine system (LNG-IUS)
    - useful if the woman also requires contraception
    - cannot be used if there is distortion of the uterine cavity
- NSAIDs e.g. mefenamic acid
- tranexamic acid
- combined oral contraceptive pill
- oral progestogen
- injectable progestogen

Treatment to shrink/remove fibroids

- medical
    - GnRH agonists may reduce the size of the fibroid but are typically used more for short-term treatment due to side-effects such as menopausal symptoms (hot flushes, vaginal dryness) and loss of bone mineral density
    - ulipristal acetate has been in the past but not currently due to concerns about rare but serious liver toxicity
- surgical
    - myomectomy: this may be performed abdominally, laparoscopically or hysteroscopically
    - hysteroscopic endometrial ablation
    - hysterectomy
- uterine artery embolization

Prognosis and complications

Fibroids generally regress after the menopause.

Some of the complications such as subfertility and iron-deficiency anaemia have been mentioned previously.

Other complications

- red degeneration - haemorrhage into tumour - commonly occurs during pregnancy

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 0 👎 0

Fibroids guidelines

Report broken link

Media

UTERINE FIBROID
OSMOSIS.org

Uterine fibroids

Osmosis - YouTube 👍 6 👎 1

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PassMedicine

Question 152 of 414

A 33-year-old white male attends his GP with a two month history of weight loss, lethargy and polydipsia. He has a past medical history of a thyroidectomy for Grave's disease, no significant family history and currently takes levothyroxine. The GP does a capillary glucose measurement, which is 18.1mmol/L and does a urinalysis revealing 2+ glucose and 2+ ketones. His blood pressure is 134/86mmHg. What is the most likely diagnosis?

	Type 2 diabetes mellitus	10%
	Addison's disease	2%
🟩	Latent Autoimmune Diabetes of Adulthood	63%
🟥	Maturity Onset Diabetes of the Young	17%
	Levothyroxine-induced diabetes mellitus	8%

Latent autoimmune diabetes of adulthood (LADA) is a disorder in which, despite the presence of islet antibodies at diagnosis of diabetes, the progression of autoimmune -cell failure is slow.

In contrast to type 2 diabetes, patients are typically younger and without an increased body habitus. In contrast to type 1 diabetes, insulin is not usually required in the early stages of the disease.

Diagnosis may be aided through a Glutamic Acid Decarboxylase (GAD) Autoantibodies test and evidence of other autoimmune diseases.

Levothyroxine is not associated with inducing diabetes. In patients with diabetes starting thyroxine, doses of antidiabetic drugs including insulin may need to be increased.

Addison's disease is associated with hypoglycaemia.

Discuss (6) Improve

Next question

Diabetes mellitus: a very basic introduction ★

Diabetes mellitus is one of the most common conditions encountered in clinical practice and represents a significant burden on the health systems of the developed world. It is now estimated that 8% of the total NHS budget is now spent on managing patients with diabetes mellitus.

What is diabetes mellitus?

Diabetes mellitus may be defined as a chronic condition characterised by abnormally raised levels of blood glucose.

Why is the management of diabetes mellitus so important?

Before the advent of insulin therapy untreated type 1 diabetes would usually result in death. Poorly treated type 1 diabetes mellitus can still result in significant morbidity and mortality (as a result of diabetic ketoacidosis). However, the main focus of diabetes management now is reducing the incidence of macrovascular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

Type	**Notes**
Type 1 diabetes mellitus (T1DM)	Autoimmune disorder where the insulin-producing beta cells of the islets of Langerhans in the pancreas are destroyed by the immune system This results in an absolute deficiency of insulin resulting in raised glucose levels Patients tend to develop T1DM in childhood/early adult life and typically present unwell, possibly in diabetic ketoacidosis
Type 2 diabetes mellitus (T2DM)	This is the most common cause of diabetes in the developed world. It is caused by a relative deficiency of insulin due to an excess of adipose tissue. In simple terms there isn't enough insulin to 'go around' all the excess fatty tissue, leading to blood glucose creeping up.
Prediabetes	This term is used for patients who don't yet meet the criteria for a formal diagnosis of T2DM to be made but are likely to develop the condition over the next few years. They, therefore, require closer monitoring and lifestyle interventions such as weight loss

Type	Notes
Gestational diabetes	Some pregnant develop raised glucose levels during pregnancy. This is important to detect as untreated it may lead to adverse outcomes for the mother and baby
Maturity onset diabetes of the young (MODY)	A group of inherited genetic disorders affecting the production of insulin. Results in younger patients developing symptoms similar to those with T2DM, i.e. asymptomatic hyperglycaemia with progression to more severe complications such as diabetic ketoacidosis
Latent autoimmune diabetes of adults (LADA)	The majority of patients with autoimmune-related diabetes present younger in life. There are however a small group of patients who develop such problems later in life. These patients are often misdiagnosed as having T2DM
Other types	Any pathological process which damages the insulin-producing cells of the pancreas may cause diabetes to develop. Examples include chronic pancreatitis and haemochromatosis. Drugs may also cause raised glucose levels. A common example is glucocorticoids which commonly result in raised blood glucose levels

Symptoms and signs

The presentation of diabetes mellitus depends very much on the type:

Type 1 DM	Type 2 DM
Weight loss Polydipsia Polyuria May present with diabetic ketoacidosis • abdominal pain • vomiting • reduced consciousness level	Often picked up incidentally on routine blood tests Polydipsia Polyuria

Remember that the polyuria and polydipsia are due to water being 'dragged' out of the body due to the osmotic effects of excess blood glucose being excreted in the urine (glycosuria).

Investigations

There are 4 main ways to check blood glucose:
- a finger-prick bedside glucose monitor
- a one-off blood glucose. This may either be fasting or non-fasting
- a HbA1c. This measures the amount of glycosylated haemoglobin and represents the average blood glucose over the past 2-3 months
- a glucose tolerance test. In this test, a fasting blood glucose is taken after which a 75g glucose load is taken. After 2 hours a second blood glucose reading is then taken

The diagnostic criteria are determined by WHO.

If the patient is symptomatic:
- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

In 2011 WHO released supplementary guidance on the use of HbA1c for the diagnosis of diabetes:
- a HbA1c of greater than or equal to 6.5% (48 mmol/mol) is diagnostic of diabetes mellitus
- a HbAlc value of less than 6.5% does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover

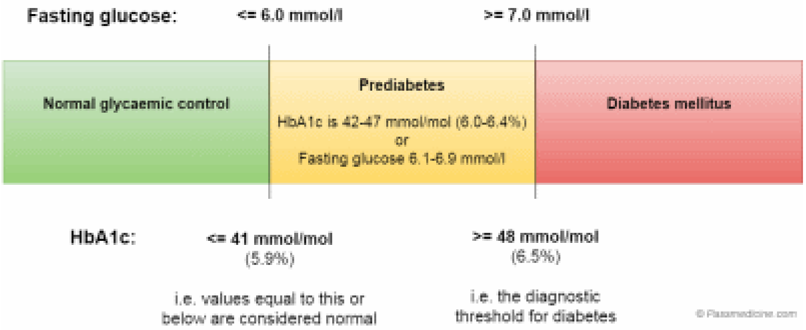
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

Management

The principle of managing diabetes mellitus are as follows:
- drug therapy to normalise blood glucose levels
- monitoring for and treating any complications related to diabetes
- modifying any other risk factors for other conditions such as cardiovascular disease

Type 1 diabetes
- patients always require insulin to control the blood sugar levels. This is because there is an absolute deficiency of insulin with no pancreatic tissue left to stimulate with drugs
- different types of insulin are available according to their duration of action

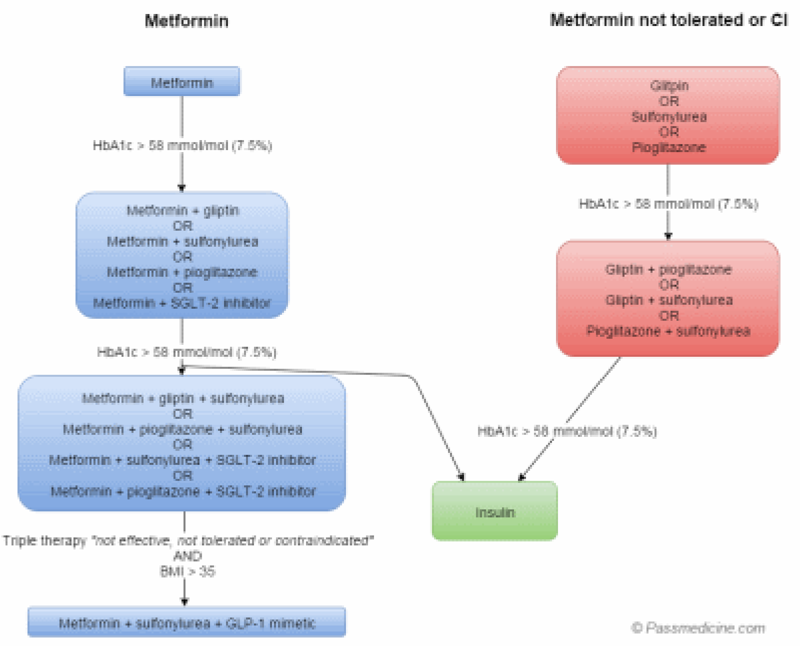
Type 2 diabetes
- the majority of patients with type 2 diabetes are controlled using oral medication
- the first-line drug for the vast majority of patients is metformin
- second-line drugs include sulfonylureas, gliptins and pioglitazone. Please see the table below for further information
- if oral medication is not controlling the blood glucose to a sufficient degree then insulin is used

The table below shows some of the main drugs used in the management of diabetes mellitus:

Drug class	Mechanism of action	Route	Main side-effects	Notes
Insulin	Direct replacement for endogenous insulin	Subcutaneous	Hypoglycaemia Weight gain Lipodystrophy	Used in all patients with T1DM and some patients with poorly controlled T2DM Can be classified according to source (analogue, human sequence and porcine) and

Drug class	Mechanism of action	Route	Main side-effects	Notes
				duration of action (short, immediate, long-acting)
Metformin	Increases insulin sensitivity Decreases hepatic gluconeogenesis	Oral	Gastrointestinal upset Lactic acidosis*	First-line medication in the management of T2DM Cannot be used in patients with an eGFR of < 30 ml/min
Sulfonylureas	Stimulate pancreatic beta cells to secrete insulin	Oral	Hypoglycaemia Weight gain Hyponatraemia	Examples include gliclazide and glimepiride
Thiazolidinediones	Activate PPAR-gamma receptor in adipocytes to promote adipogenesis and fatty acid uptake	Oral	Weight gain Fluid retention	Only currently available thiazolidinedione is pioglitazone
DPP-4 inhibitors (-gliptins)	Increases incretin levels which inhibit glucagon secretion	Oral	Generally well tolerated but increased risk of pancreatitis	
SGLT-2 inhibitors (-gliflozins)	Inhibits reabsorption of glucose in the kidney	Oral	Urinary tract infection	Typically result in weight loss
GLP-1 agonists (-tides)	Incretin mimetic which inhibits glucagon secretion	Subcutaneous	Nausea and vomiting Pancreatitis	Typically result in weight loss

NICE provide guidelines on how drug therapy should be used in T2DM:


Metformin
Metformin not tolerated or CI
Metformin
HbA1c > 58 mmol/mol (7.5%)
Metformin + gliptin OR Metformin + sulfonylurea OR Metformin + pioglitazone OR Metformin + SGLT-2 inhibitor
HbA1c > 58 mmol/mol (7.5%)
Metformin + gliptin + sulfonylurea OR Metformin + pioglitazone + sulfonylurea OR Metformin + sulfonylurea + SGLT-2 inhibitor OR Metformin + pioglitazone + SGLT-2 inhibitor
Triple therapy "not effective, not tolerated or contraindicated" AND BMI > 35
Metformin + sulfonylurea + GLP-1 mimetic
Gliptin OR Sulfonylurea OR Pioglitazone
HbA1c > 58 mmol/mol (7.5%)
Gliptin + pioglitazone OR Gliptin + sulfonylurea OR Pioglitazone + sulfonylurea
HbA1c > 58 mmol/mol (7.5%)
Insulin
© Passmedicine.com

*common in exams, much less common in clinical practice

Next question

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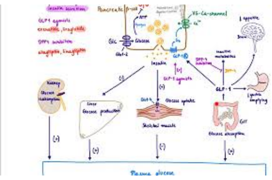
Media

DIABETES MELLITUS
OSMOSIS.org

Diabetes mellitus (type 1, type 2) & diabetic ketoacidosis (DKA) - causes & symptoms

Osmosis - YouTube 👍 3 👎 1



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 7 👎 3

Drugs for diabetes

Speed Pharmacology - YouTube 👍 3 👎 3

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 1 👎 2

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Score: **23.7%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗

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Question 153 of 414 ✗

A 6-year-old South Sudanese boy is admitted progressive worsening of his hearing loss. His mother is extremely concerned with his lack of progress at school. Systems review reveals a 2-month history of malaise, arthralgia and constipation. He has a past medical history of deafness. On examination he has dry skin and thin hair; there were no thyroid eye signs, no ophthalmoplegia and no myxoedema. He appears to have a smooth symmetrically enlarged goitre, which is not painful.

Thyroid function tests:

Thyroid stimulating hormone	5.7 (mu/l)
Free T4	9 pmol/l
Total T4	67 nmol/l

Which of the following causes of hypothyroidism is the patient suffering from?

	Hashimoto's thyroiditis	9%
🟥	Iodine deficiency	24%
🟩	Pendred syndrome	62%
	Thyroid agenesis	3%
	Atrophic hypothyroidism	2%

The patient is suffering from mild signs of hypothyroidism and progressive bilateral deafness. Out of the following answers only Pendred syndrome presents with signs of deafness and hypothyroidism.

Discuss (6) Improve

Next question

Pendred's syndrome

Pendred is an autosomal recessive genetic disorder that is characterised by bilateral sensorineural deafness, with mild hypothyroidism and a goitre. The patients tend to present with progressive hearing loss and delay in academic progression. Often head trauma tends to make the sensorineural deafness worse, leading to patients having to avoid contact sports.

In Pendred syndrome there is a defect in the organification of iodine, leading to dyshormonogenesis. However thyroid symptoms in pendred syndrome are often mild and patients are often clinically euthyroid, presenting only with a goitre. Thyroid function tests are also often normal, requiring the perchlorate discharge test to aid diagnosis.

The syndrome can be diagnosed via genetic testing (Pendred syndrome (PDS) gene, chromosome 7), audiometry and MRI imaging to look for characteristic one and a half turns in the cochlea, compared to the normal two and a half turns.

Treatment is with thyroid hormone replacement and cochlear implants.

Next question

Textbooks

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Score: **23.5%**

1 ✓
2 ✓
3 ✓

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Question 154 of 414 ✗

A 65-year-old woman presents to her general practitioner with reports of urinary frequency and urgency. She occasionally has episodes of incontinence when she does not reach the bathroom on time. She does not notice incontinence when coughing, straining or laughing. She has three children, all born by vaginal delivery. One of the pregnancies was delivered with the aid of a forceps.

The examination is unremarkable.

Given the likely diagnosis, what is the most appropriate management?

🟩	Bladder retraining	42%
🟥	Duloxetine	8%
	Mirabegron	15%
	Pelvic floor muscle re-training	29%
	Tolterodine	5%

Urinary incontinence - first-line treatment:

- urge incontinence: bladder retraining
- stress incontinence: pelvic floor muscle training

Important for me Less important

Bladder retraining is the correct answer. The patient presents with symptoms of urge incontinence (frequency and urgency). This first-line management of this condition is bladder retraining.

Duloxetine is incorrect. This is a norepinephrine and serotonin uptake inhibitor that can be used for stress incontinence should pelvic floor muscle re-training fail.

Mirabegron is incorrect. This is a beta-3-agonist that can be used to treat overactive bladder should bladder re-training and antimuscarinics fail.

Pelvic floor muscle re-training is incorrect. This is the first-line management of stress incontinence.

While she has had three children and instrumental delivery, she does not have symptoms of stress incontinence i.e. incontinence provoked by activities such as straining, laughing and coughing and therefore this is incorrect.

Tolterodine is incorrect. This is an antimuscarinic medication that can be used to manage urge incontinence if conservative measures fail.

Discuss (2) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification

- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days

- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
    - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
    - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
    - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
    - a combined noradrenaline and serotonin reuptake inhibitor
    - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

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Media

URINARY
INCONTINENCE

Urinary incontinence

Osmosis - YouTube 👍 0 👎 1

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Score: **23.4%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗

PassMedicine

Question 155 of 414 ✗

A 38-year-old male presents with chronic fatigue, headaches, and poor hearing. He reports struggling a work with seemingly decreased memory and difficulty concentrating. On direct questioning, the patient confirms he has gained a significant amount of weight since his symptoms began.

On examination, the patient has cool extremities and a cranial nerve exam reveals bitemporal hemianopia.

Blood tests are taken:

	Patient's results	Reference range
8 am ACTH	5 pg/mL	10-50
Prolactin	2 µg/L	<17
TSH	0.2 mIU/L	0.4-4.0
FSH	2 IU/L	4-25
LH	4 IU/L	6-23
GH	0 µg/L	< 5

What is the most likely diagnosis?

🟥 Cushing disease	4%
Sheehan's syndrome	12%
🟩 Pituitary adenoma	78%
Primary hypothyroidism	3%
Prolactinomas	3%

Non-functioning pituitary tumours present with hypopituitarism and pressure effects

Important for me Less important

This patient has presented with features in keeping with a non-functioning pituitary adenoma. There is evidence of dura stretching around the pituitary fossa and compression of the optic chiasm causing headaches and visual field defects. Blood hormone investigations show hypopituitarism resulting from compression of the normal functioning pituitary gland and this accounts for the patient's symptoms of hypothyroidism.

Cushing's disease is characterised by increased adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary, normal resulting from an ACTH-producing pituitary adenoma. Although this would account for the compression symptoms and depletion of other hormones the patient's ACTH levels are low and there is no evidence of the classic Cushing syndrome features (i.e. hypertension, fat redistribution).

Sheehan's syndrome is a condition resulting in hypopituitarism however it is specifically caused by ischaemic necrosis due to post-partum blood loss and hypovolemic shock. It is an acute condition and is not associated with optical chiasm compression.

Primary hypothyroidism is due to an inadequate function of the thyroid gland itself; a reduction in the T3 and T4 production. This would explain the patient's symptoms of fatigue, poor concentration and weight gain, however, you would expect an increased TSH level due to positive feedback secondary to a lack of T3 and T4. Other hormone levels should also be unaffected.

A prolactinoma would produce similar symptoms of headache, compression of the chiasm and hypopituitarism. However, the patient's prolactin level is low and therefore his tumour is non-functioning i.e. not producing prolactin.

Discuss (4) Improve

Next question

Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:
- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)
- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
  - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:
- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:
- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of
- medical therapy:
  - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
  - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas
  - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery

  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Patient.info 👍 7 👎 0

Pituitary tumours review

Report broken link

Score: **23.2%**

1 ✓
2 ✓
3 ✓

Question 156 of 414 ✗

A 56-year-old man is reviewed in the diabetes clinic for a routine follow-up appointment. He has a past medical history of type-2 diabetes mellitus, obesity (BMI of 38kg/m^2), heart failure, hypertension, and hyperlipidaemia. His current medication includes metformin, dapagliflozin, sitagliptin, atorvastatin, furosemide, ramipril, and bisoprolol.

On review, his most recent HbA1c is 60mmol/mol. He says his compliance with all his medications is good. His weight upsets him greatly; he has recently lost a little and is keen to lose more.

What is the most appropriate course of action?

No medication changes required	7%
Replace sitagliptin with gliclazide	7%
Replace sitagliptin with liraglutide	69%
Replace sitagliptin with pioglitazone	4%
Start insulin	13%

TD2M: if a triple combination of drugs has failed to reduce HbA1c then switching one of the drugs for a GLP-1 mimetic is recommended, particularly if the BMI > 35

Important for me Less important

Replace sitagliptin with liraglutide is correct. This patient has poorly controlled diabetes despite being on three oral antidiabetic agents already. Options at this point include insulin therapy or substituting one of his existing antidiabetic agents for a GLP-1 analogue. Given this patient's raised BMI and his desire to lose weight, switching one of his medications for a GLP-1 analogue is the most appropriate option.

No medication changes required is incorrect. This patient's HbA1c is 60mmol/mol - above the cut-off of 58mmol/mol, at which further medication changes are required. Making no changes is, therefore, incorrect.

Replace sitagliptin with gliclazide is incorrect. This patient is on triple oral antidiabetic therapy, and yet his HbA1c is still raised. Current guidance suggests the most appropriate step is switching to insulin therapy or swapping one of the existing medications for a GLP-1 analogue. There is no rationale for switching one of this patient's existing oral antidiabetic agents for another.

Replace sitagliptin with pioglitazone is incorrect. Current guidance recommends that a patient on triple oral antidiabetic therapy whose HbA1c is over 58mmol/mol requires either insulin or a GLP-1 analogue rather than substituting one oral agent for another. Additionally, pioglitazone is contraindicated in patients with heart failure.

Start insulin is incorrect. This patient would indeed qualify for insulin therapy: already on triple oral antidiabetic therapy, and yet the HbA1c is still raised. Although insulin is an option at this stage, this patient's BMI is > 35kg/m^2, and therefore, a GLP-1 analogue like liraglutide would be favored over insulin as it promotes weight loss.

👍 👎 Discuss Improve

Next question

Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

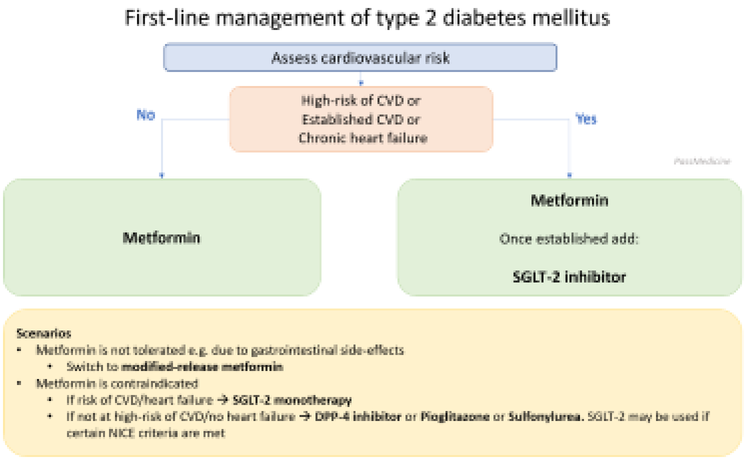
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor
Scenarios
Metformin is not tolerated e.g. due to gastrointestinal side-effects
Switch to modified-release metformin
Metformin is contraindicated
If risk of CVD/heart failure → SGLT-2 monotherapy
If not at high-risk of CVD/no heart failure → DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

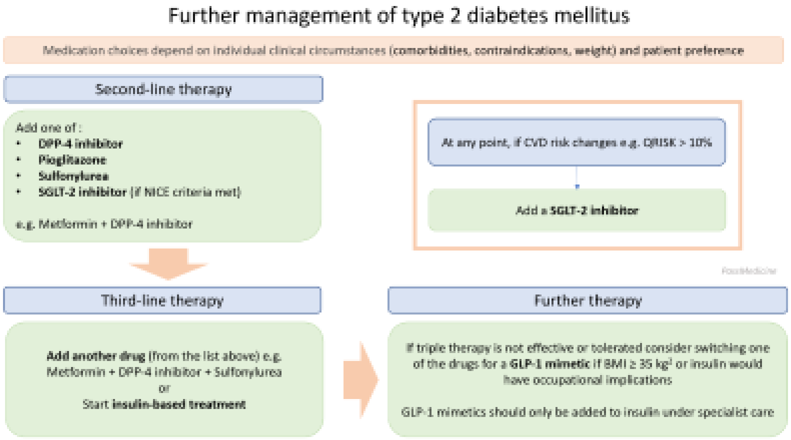
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met



Medication choices depend on individual clinical circumstances (**comorbidities, contraindications, weight) and patient preference**

Add one of :
- **DPP-4 inhibitor**
- **Pioglitazone**
- **Sulfonylurea**
- **SGLT-2 inhibitor** (if NICE criteria met)

e.g. Metformin + DPP-4 inhibitor

At any point, if CVD risk changes e.g. QRISK > 10%

Add a **SGLT-2 inhibitor**

Add another drug (from the list above) e.g.
Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start **insulin-based treatment**

If triple therapy is not effective or tolerated consider switching one of the drugs for a **GLP-1 mimetic** if BMI ≥ 35 kg^2 or insulin would have occupational implications

GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:
- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:
- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:
- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

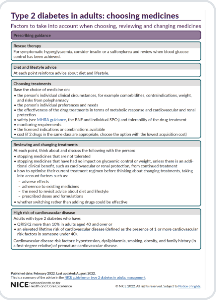
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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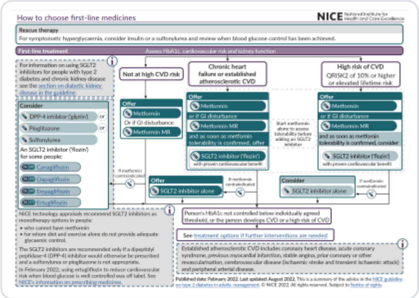

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk

Offer
Metformin
Or if GI disturbance
Metformin MR

If metformin contraindicated

Chronic heart failure or established atherosclerotic CVD

Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin')
with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk

Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin')
with proven cardiovascular benefit

If metformin contraindicated

Offer
SGLT2 inhibitor alone

If metformin contraindicated

Consider
SGLT2 inhibitor alone

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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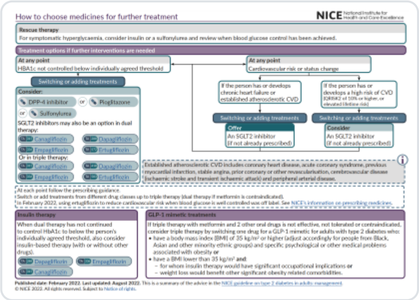

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Or in triple therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD

Switching or adding treatments

Offer
An SGLT2 inhibitor
(if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)

Switching or adding treatments

Consider
An SGLT2 inhibitor
(if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity-related comorbidities.

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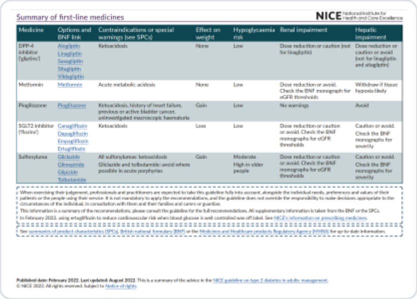

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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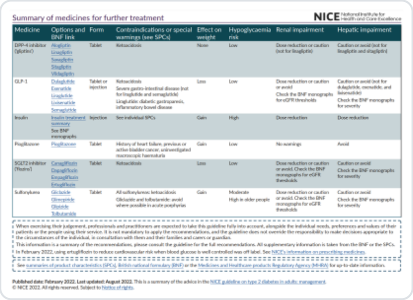

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

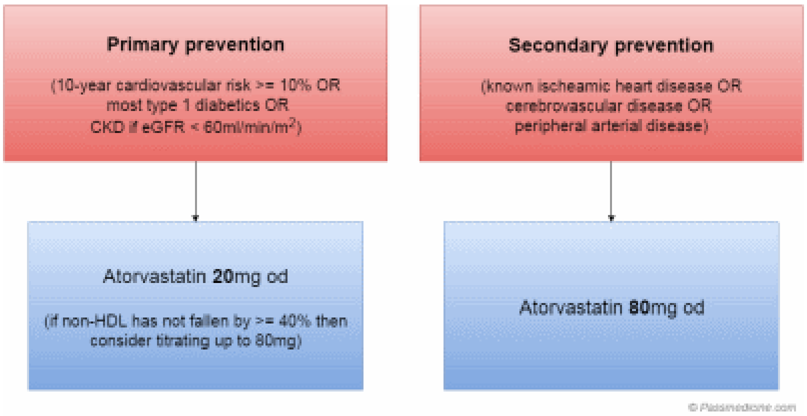
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 3 0

2014 Lipid modification guidelines

7 minute medics 11 4

Basics of type 2 diabetes - podcast

SIGN 4 2

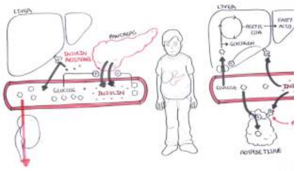
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media

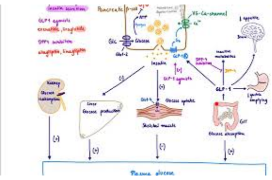


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

Report broken media

Score: **23.1%**

1 ✓
2 ✓
3 ✓

PassMedicine

Question 157 of 414 ✗

An 85-year-old comes for review. She has recently had private health screening and has been advised to see a doctor regarding her thyroid function tests (TFTs).

TSH	9.2 mU/L
Free thyroxine	14 pmol/L

She is currently well and asymptomatic. What is the most appropriate management?

	Start levothyroxine	18%
	Start carbimazole	3%
	Order a thyroid ultrasound scan	10%
🟥	Start levothyroxine + carbimazole ('block and replace')	4%
🟩	Repeat TFTs in a few months time	65%

This patient has subclinical hypothyroidism. By both the TSH and age criteria advocated by NICE Clinical Knowledge Summaries she should be monitored for now.

Discuss (4) Improve

Next question

Subclinical hypothyroidism

Basics

- TSH raised but T3, T4 normal
- no obvious symptoms

Significance

- risk of progressing to overt hypothyroidism is 2.5% per year (higher in men)

- risk of progressing to overt hypothyroidism is 2-5% per year (higher in men)
- risk increased by the presence of thyroid autoantibodies

Management

Not all patients require treatment. NICE Clinical Knowledge Summaries (CKS) have produced guidelines. Note that not all patients will fall within the age boundaries given and hence these are guidelines in the broader sense.

TSH is > 10mU/L and the free thyroxine level is within the normal range
- consider offering levothyroxine if the TSH level is > 10 mU/L on 2 separate occasions 3 months apart

TSH is between 5.5 - 10mU/L and the free thyroxine level is within the normal range
- if < 65 years consider offering a 6-month trial of levothyroxine if:
    - the TSH level is 5.5 - 10mU/L on 2 separate occasions 3 months apart,*and*
    - there are symptoms of hypothyroidism
- in older people (especially those aged over 80 years) follow a 'watch and wait' strategy is often used
- if asymptomatic people, observe and repeat thyroid function in 6 months

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 5 👎 1

PassMedicine

Question 158 of 414 ✗

A 42-year-old woman attends the clinic with sweating, palpitations, weight loss and diarrhoea. On examination, she has a painless goitre.

Blood results are as follows:

Thyroid stimulating hormone (TSH)	0.1 mU/L	(0.5-5.5)
Free thyroxine (T4)	32.6 pmol/L	(9.0 - 18)

You start the patient on carbimazole.

How does this medication treat the underlying diagnosis?

	Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on calcitonin	5%
🟩	Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin	77%
	Inhibits binding of T3 and T4 to thyroid hormone receptors	3%
	Inhibits the peripheral conversion of T4 to T3 by inhibiting 5'-deiodinase	13%
🟥	Inhibits thyroid hormone secretion	2%

Carbimazole blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production

Important for me Less important

Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin is correct. Carbimazole is an antithyroid medication used to treat hyperthyroidism, a condition in which the thyroid gland produces too much thyroid hormone. The drug achieves this by blocking the action of an enzyme called thyroid peroxidase in the thyroid gland. This enzyme normally plays a key role in the production of thyroid hormones by coupling and iodinating the tyrosine residues on thyroglobulin, a protein within the thyroid gland that serves as a precursor for these hormones. By blocking this process, carbimazole reduces the production of thyroid hormones, helping to restore normal levels in the body.

Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on calcitonin is incorrect. Calcitonin is involved in calcium haemostasis and plays no role in thyroid hormone production.

Inhibits binding of T3 and T4 to thyroid hormone receptors is incorrect. Drugs which exhibit thyroid receptor antagonism include amiodarone.

Inhibits the peripheral conversion of T4 to T3 by inhibiting 5'-deiodinase is incorrect. This is one of the mechanisms of action of propylthiouracil.

Inhibits thyroid hormone secretion is incorrect. This is the mechanism of action of Lugol's iodine which acutely inhibits hormonal secretion due to the Wolff-Chaikoff effect. In normal individuals, excess iodide inhibits thyroid hormone synthesis. The proposed mechanism is that iodopeptide(s) are formed that temporarily inhibit thyroid peroxidase (TPO) mRNA and protein synthesis and, therefore, thyroglobulin iodinations.

👍 👎 Discuss Improve

Next question

Carbimazole ★

Carbimazole is used in the management of thyrotoxicosis. It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.

Mechanism of action

- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production
- in contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5'-deiodinase which reduces peripheral conversion of T4 to T3

Adverse effects

- agranulocytosis
- crosses the placenta, but may be used in low doses during pregnancy

Next question

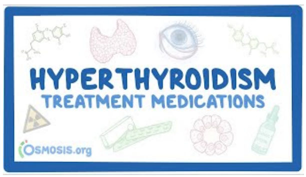
B I A

Textbooks

High-yield textbook

Extended textbook

Media


HYPERTHYROIDISM
TREATMENT MEDICATIONS
Osmosis.org

Hyperthyroidism treatment medications

Osmosis - YouTube 13 3

Report broken media

Score: **22.8%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓

PassMedicine

Question 159 of 414 ✓

An obese 48-year-old man presents with lethargy and polydipsia. What is the minimum HbA1c that would be diagnostic of type 2 diabetes mellitus?

Cannot use HbA1c for diagnosis	5%
6.0% (42 mmol/mol)	3%
6.3% (45 mmol/mol)	3%
[✓ 6.5% (48 mmol/mol)]	79%
7.0% (53 mmol/mol)	10%

Diabetes mellitus - HbA1c of 48 mmol/mol (6.5%) or greater is diagnostic

Important for me Less important

The correct answer is **6.5% (48 mmol/mol)**. According to the World Health Organisation (WHO) and the National Institute for Health and Care Excellence (NICE) guidelines in the UK, an HbA1c level of 6.5% or above is diagnostic of type 2 diabetes mellitus. This test measures the average blood glucose control over the past 2-3 months, providing a longer-term trend, similar to an 'average' of blood glucose levels.

The option **Cannot use HbA1c for diagnosis** is incorrect because HbA1c testing is indeed used for diagnosing type 2 diabetes. It provides an overview of long-term blood glucose control and has been found to be a reliable method for diagnosing this condition.

The options **6.0% (42 mmol/mol)** and **6.3% (45 mmol/mol)** are also incorrect. Although these values are higher than normal, they fall into the category of 'prediabetes', which represents a high risk for future development of diabetes but does not meet the threshold for a definitive diagnosis.

Finally, while an HbA1c level of **7.0% (53 mmol/mol)** would certainly confirm a diagnosis of type 2 diabetes, it's not the minimum value necessary for diagnosis as per WHO and NICE guidelines - hence, this option is also incorrect.

Discuss (2) Improve

Next question

Diabetes mellitus (type 2): diagnosis ★

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic: CKS

- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

When HbA1c is used for the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis: CKS

- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

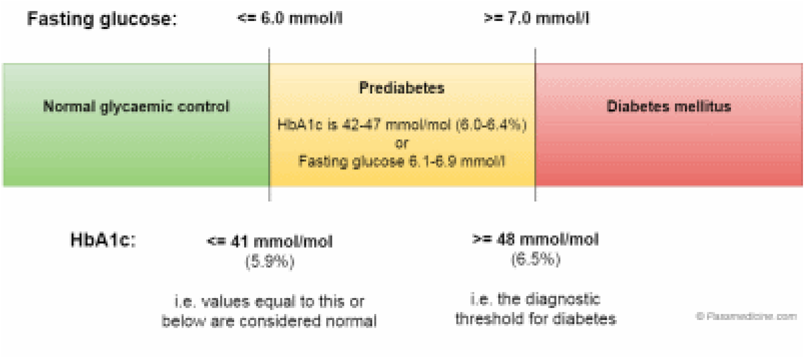

Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
© Passmedicine.com

Diagram showing the spectrum of diabetes diagnosis

Impaired fasting glucose and impaired glucose tolerance

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:
- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 2 👎 1

Type 2 diabetes mellitus: diagnosis

NICE 👍 2 👎 2

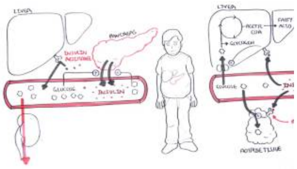
2022 Type 2 diabetes guidelines

Diabetes UK 👍 3 👎 4

New diagnostic criteria for diabetes

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 8 👎 1

Report broken media

Score: **23.3%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓

PassMedicine

Question 160 of 414 ✗

A 52-year-old has a fasting lipid profile checked as part of an annual occupational health check. Combined with his blood pressure and current smoking status his 10-year risk of cardiovascular disease is calculated to be 23% percent. Following appropriate counselling he chooses to start atorvastatin 20mg. He is followed up 3 months later when a full lipid profile is repeated. What should his target be?

🟩	A greater than 40% reduction in non-HDL cholesterol	72%
	Total cholesterol < 5 mmol/l	8%
	Target cholesterol is inappropriate in this situation	7%
🟥	Total cholesterol < 4 mmol/l	7%
	Total cholesterol:HDL ratio < 4	6%

In the primary prevention of CVD using statins aim for a reduction in non-HDL cholesterol of > 40%

Important for me Less important

The correct answer is **A greater than 40% reduction in non-HDL cholesterol**. According to the UK guidelines, patients with a 10-year risk of cardiovascular disease ≥10% should be considered for statin therapy. The primary target for lipid-lowering therapy in these patients is to achieve a greater than 40% reduction in non-HDL cholesterol. This approach focuses on reducing the absolute risk of cardiovascular events rather than achieving specific lipid targets.

The option **Total cholesterol < 5 mmol/l** is incorrect because it does not take into account the patient's baseline lipid levels and individual risk factors. A fixed target like this may not provide adequate risk reduction for all patients, especially those at higher risk of cardiovascular events.

Target cholesterol is inappropriate in this situation is also incorrect. Targeting cholesterol levels is an important part of managing patients with increased cardiovascular risk, as lowering cholesterol has been shown to reduce the incidence of coronary heart disease and stroke. In this case, where the patient has a 23% 10-year risk of cardiovascular disease, addressing his cholesterol levels through statin therapy like atorvastatin is appropriate.

The option **Total cholesterol < 4 mmol/l** is incorrect for similar reasons as the 'Total cholesterol < 5 mmol/l' option. It represents a fixed target that may not be applicable to all individuals and does not focus on the percentage reduction in non-HDL cholesterol which better reflects the patient's overall cardiovascular risk.

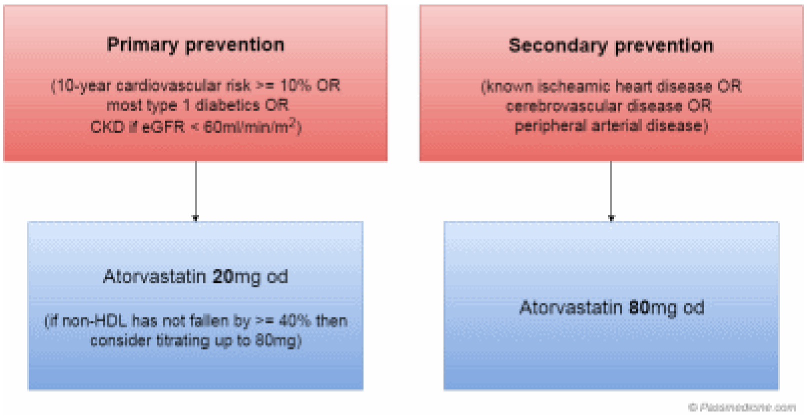
Lastly, **Total cholesterol:HDL ratio < 4** is also an incorrect answer. Although maintaining a favourable total cholesterol:HDL ratio can contribute to reducing cardiovascular risk, it should not be used as the primary target for lipid-lowering therapy. Instead, focusing on achieving a >40% reduction in non-HDL cholesterol allows for more personalized treatment goals based on each patient's individual risk factors and baseline lipid levels.

Discuss (3) Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischaemic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years.

Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation

- smokers should be encouraged to quit

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 9 👎 6

2014 Lipid modification guidelines

Clinical Knowledge Summaries 👍 4 👎 3

Managing lipids in type 2 diabetes

Report broken link

Score: **23.1%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗

PassMedicine

← Question 161 of 414 ✗ ⚐ →

A 24-year-old is seen in the antenatal clinic for their first-trimester review. she reports feeling well with no specific issues.

As the patient had several complications in her first pregnancy she has several screening blood tests performed including thyroid function testing. Selected aspects of these investigations are shown below.

TSH	4.2 mIU/L	0.4-4.0
Thyroxine (T4)	220 nmol/L	64-155
Free thyroxine (fT4)	15 pmol/L	12.0-21.9

The patient denies any symptoms in keeping with thyrotoxicosis and examination is normal.

A rise in what thyroid-associated protein primarily causes these findings?

	Antithyroid peroxidase antibodies	9%
🟥	Thyroglobulin	12%
🟩	Thyroid binding globulin	67%
	Thyroid stimulating hormone	6%
	Thyrotropin-releasing hormone	6%

Raised total T3 and T4 but normal fT3 and fT4 suggest high concentrations of thyroid binding globulin, which can be seen during pregnancy

Important for me Less important

Elevated oestrogen levels produced in pregnancy stimulate the expression of **thyroid binding globulin** (TBG) from the liver. As TBG binds to free thyroxine (fT4) and free triiodothyronine (fT3), an increase in TBG results in an initial lowering of fT4 and fT3. This in turn causes a secondary increase in thyroid-stimulating hormone (TSH). The net result is a new equilibrium between free and bound thyroid hormones with an increase in bound-T3 and T4 but an overall unaffected fT3 and fT4 level. As it's the fT4 and fT3 that are responsible for clinic features of thyrotoxicosis these cases rarely produce clinical signs or symptoms, nor do they require treatment.

Antithyroid peroxidase antibodies are specific for the autoantigen TPO in the thyroid and are the most common antithyroid autoantibody. These antibodies are present in approximately 90% of Hashimoto's thyroiditis, 75% of Grave's disease, and 10-20% of nodular goitre cases. Antithyroid antibodies do not occur as a result of pregnancy.

Thyroglobulin (Tg) is only found and used within the thyroid gland following its production in the follicular cells. Tg acts as a substrate for the synthesis of T3 and T4, as well as storage of the inactive forms of the thyroid hormones. Tg levels can increase in the final trimester of pregnancy when compared to non-pregnancy patients however it generally remains within the normal range. Also, this mild rise is in response to an increase in TSH levels and therefore would not be the initial cause in this case.

Thyroid stimulating hormone (TSH) is responsible for increasing the production of T3 and T4. Although a raised TSH level can be seen in pregnancy this is a secondary effect caused by the increase in TBG and therefore is not the primary issue.

Thyrotropin-releasing hormone (TRH) is produced in the hypothalamus and stimulates the releases of TSH as well as prolactin. Again TRH can increase in pregnancy but only as a result of an increase in TBG and therefore it is not the initial cause.

Discuss Improve

Next question

Pregnancy: thyroid problems

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management

- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

High-yield textbook

Extended textbook

Links

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Question 162 of 414 ✓

A 35-year-old female who has recently being diagnosed with Grave's disease presents for review 3 months after starting a 'block and replace' regime with carbimazole and thyroxine. She is concerned about developing thyroid eye disease. What is the best way that her risk of developing thyroid eye disease can be reduced?

Reduce alcohol intake	5%
A diet rich in omega-3 fatty acids	9%
Regular exercise	2%
Stop smoking	81%
Lose weight	3%

Smoking is the most important modifiable risk factor for the development of thyroid eye disease

Important for me Less important

The correct answer is **Stop smoking**. Smoking cessation is the most effective way to reduce the risk of developing thyroid eye disease (TED) in patients with Graves' disease. This is because smoking has been shown to increase the severity and progression of TED, as well as reduce the effectiveness of its treatment.

Reduce alcohol intake is not a correct option. While excessive alcohol consumption can have numerous negative health effects, there is no established link between alcohol intake and the risk or severity of TED.

A diet rich in **omega-3 fatty acids** can have various health benefits, including potentially reducing inflammation and improving heart health. However, while some studies suggest that omega-3 fatty acids may help improve dry eye symptoms - a condition that can occur alongside TED - there's no direct evidence to suggest they can prevent or reduce the risk of developing TED itself.

Regular exercise is generally beneficial for overall health and well-being, but it does not specifically reduce the risk of developing TED in patients with Graves' disease.

Lastly, **Lose weight**, although beneficial for general health and certain conditions such as type 2 diabetes or cardiovascular diseases, there's no specific evidence suggesting that weight loss alone could decrease the risk or severity of TED. It should be noted that hyperthyroidism due to Graves' disease often leads to weight loss rather than gain.

👍 👎 Discuss (1) Improve

Next question

Thyroid eye disease ★

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eyelids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

Management

- smoking cessation
- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy

- surgery

Complications

Exposure keratopathy

- this is the most common complication of thyroid eye disease
- due to eyelid retraction and proptosis (exophthalmos) → cornea becomes excessively exposed, disrupting the normal tear film → dryness, irritation, and corneal ulceration
- symptoms include foreign body sensation, pain, and photophobia
- in severe cases, it can lead to corneal scarring and vision impairment.

Optic neuropathy

- one of the most serious complications of thyroid eye disease
- occurs when enlarged extraocular muscles compress the optic nerve at the apex of the orbit → a reduction in visual acuity, colour vision deficits, and visual field defect
- it requires urgent medical intervention to prevent permanent vision loss.

Strabismus and diplopia

- fibrosis and enlargement of the extraocular muscles can result in restrictive strabismus → misalignment of the eyes → double vision (diplopia)
- this not only affects visual function but can also significantly impair the quality of life.

Monitoring patients with established thyroid eye disease

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Consensus Statement of the European Group on Graves' Orbitopathy 👍 2 👎 1

Management of Graves' Orbitopathy

Report broken link

Score: **23.5%**

1	✓
2	✓
3	✓
4	✗
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12	✓
13	✗
14	✓
15	✗
16	✗
17	✓
18	✗

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Question 163 of 414

A 55-year-old woman attends the emergency department with abdominal pain. She complains of right-sided loin pain which radiates to her groin. She is otherwise well. She has a past medical history of Sjogren's syndrome. On examination, you note right-sided renal angle tenderness.

Blood results are as follows:

Hb	126 g/L	Male: (135-180) Female: (115 - 160)
Platelets	245 * 10^9/L	(150 - 400)
WBC	6.2 * 10^9/L	(4.0 - 11.0)
Na^+	136 mmol/L	(135 - 145)
K^+	2.5 mmol/L	(3.5 - 5.0)
Cl^-	120 mmol/L	(96 - 106)
Urea	6.9 mmol/L	(2.0 - 7.0)
Creatinine	56 µmol/L	(55 - 120)
Bicarbonate	14 mmol/L	(23 - 29)
pH	7.28	(7.35 - 7.45)
Glucose	22.5 mmol/L	(4 - 7)
CRP	2 mg/L	(< 5)

What is the most likely diagnosis?

	Addison's disease	3%
🟥	Diabetic ketoacidosis (DKA)	13%
🟩	Distal renal tubular acidosis	60%
	Proximal renal tubular acidosis	18%
	Type 4 renal tubular acidosis	6%

Distal renal tubular acidosis can cause calcium phosphate renal stones and is linked to Sjogrens syndrome

Important for me Less important

The patient has a metabolic acidosis as indicated by the low serum bicarbonate. The anion gap (AG) is a derived variable primarily used for the evaluation of metabolic acidosis to determine the presence of unmeasured anions. The normal anion gap varies with different assays but is typically 4 to 12 mmol/L.

The anion gap = (Na + K) - (Cl + HCO3) = (136 + 2.5) - (120 + 14) = 4.5.

Thus the patient has a normal anion gap metabolic acidosis (NAGMA).

Causes of NAGMA include ('ABCD'):

- Addison's
- Bicarbonate loss: GI (e.g. diarrhoea) or renal (e.g. renal tubular acidosis)
- Chloride excess
- Diuretics (e.g. acetazolamide)

Causes of high anion gap metabolic acidosis (HAGMA) include:

- Lactate
- Toxins (e.g. methanol, paracetamol, propylene glycol)
- Ketones
- Renal failure

Distal renal tubular acidosis is correct. The presence of kidney stones, hypokalemia, NAGMA, and a past medical history of Sjogren's favour the diagnosis of distal RTA.

Addison's disease is incorrect. Although this can also cause a NAGMA, hyperkalemia would be expected as a consequence of hypoaldosteronism. Furthermore, patients with Addison's will often be hypoglycaemic.

Diabetic ketoacidosis (DKA) is incorrect. Although the patient is significantly hyperglycaemia and likely has undiagnosed diabetes mellitus, the presence of ketones would result in a HAGMA.

Proximal renal tubular acidosis is incorrect. This can also present with hypokalemia and NAGMA, however, there is not an association with Sjogren's making this a less likely diagnosis.

Type 4 renal tubular acidosis is incorrect. Although diabetes is a cause of type 4 RTA, this condition would be associated with hyperkalemia in contrast to the hypokalemia demonstrated in this case.

👍 👎 Discuss (1) Improve

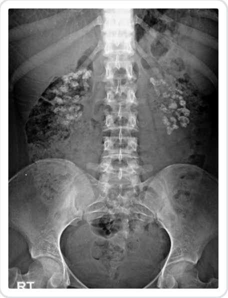
Next question

Renal tubular acidosis ★

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion

- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

Textbooks

High-yield textbook

Extended textbook

Media

Renal tubular acidosis

DirtyUSMLE - YouTube 👍 177 👎 4

Renal tubular acidosis

Osmosis - YouTube 👍 39 👎 3

Report broken media

Score: **23.3%**

1 ✓
2 ✓
3 ✓

PassMedicine

← Question 164 of 414 ✓ →

A 42-year-old man presents to his GP feeling generally unwell. For the past three months he has been experiencing daily frontal headaches which have not been helped by regular paracetamol. He has also noticed some unusual symptoms such as his wedding ring no longer fitting, his shoe size apparently increasing and a small amount of milky discharge from both nipples. On examination his blood pressure is 168/96 mmHg. What is the most likely diagnosis?

Phaeochromocytoma	3%
Cushing's syndrome	2%
Diabetes insipidus	0%
Macroprolactinoma	19%
Acromegaly	76%

Discuss (2) Improve

Next question

Acromegaly: features ★

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic.

Features

- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin: caused by sweat gland hypertrophy
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea

- 6% of patients have MEN-1

Complications

- hypertension
- diabetes (>10%)
- cardiomyopathy
- colorectal cancer

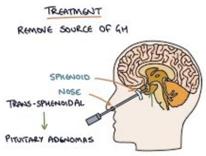
Next question

Textbooks

High-yield textbook

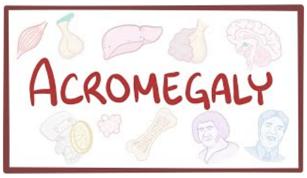
Extended textbook

Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 24 👎 1


ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 12 👎 1

PassMedicine

← Question 165 of 414 ✗ ⚐ →

A 46-year-old man with suspected diabetes mellitus has an oral glucose tolerance test, following the standard WHO protocol. The following results are obtained:

Time (hours)	Blood glucose (mmol/l)
0	5.7
2	7.6

How should these results be interpreted?

🟩 Normal	41%
Impaired fasting glucose and impaired glucose tolerance	10%
Diabetes mellitus	5%
🟥 Impaired glucose tolerance	34%
Impaired fasting glucose	10%

Both the fasting and two-hour glucose are within normal limits.

👍 👎 Discuss (2) Improve

Next question

Diabetes mellitus (type 2): diagnosis ★

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic: CKS

- fasting glucose greater than or equal to 7.0 mmol/l

- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

When HbA1c is used for the diagnosis of diabetes:
- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis: **CKS**
- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

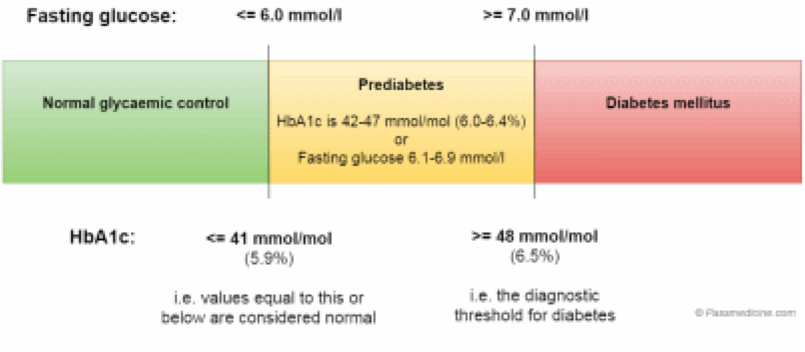

Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

Impaired fasting glucose and impaired glucose tolerance

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:

- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 2 👎 1

Type 2 diabetes mellitus: diagnosis

NICE 👍 2 👎 2

2022 Type 2 diabetes guidelines

Diabetes UK 👍 3 👎 4

New diagnostic criteria for diabetes

Report broken link

Media

PassMedicine

Question 166 of 414 ✕

A 32-year-old Caucasian woman who is 25 weeks pregnant with her first child presents to antenatal clinic. She had been invited to attend screening for gestational diabetes on account of her booking BMI, which was $33kg/m^2$. Prior to her pregnancy, she had been fit and well, and had no personal or family history of diabetes mellitus. She does not take any regular medications, and has no known allergies.

She undergoes an oral glucose tolerance test (OGTT), the results of which are as follows:

Fasting glucose	6.8mmol/L
2-hour glucose	7.6mmol/L

An ultrasound scan does not show any fetal abnormalities or hydramnios. She is given advice about diet and exercise, and undergoes a repeat OGTT two weeks later, at which point she is started on metformin due to persistent impaired fasting glucose.

After taking metformin for two weeks, she undergoes another OGTT, with results shown below:

Fasting glucose	5.9mmol/L
2-hour glucose	7.1mmol/L

Which of the following is the most appropriate next step in the management of her glycaemic control?

No changes to current treatment	25%
Switch metformin to modified-release metformin	4%
Stop metformin, add insulin	11%
Add insulin	59%
Add a sulfonylurea	1%

In gestational diabetes, if blood glucose targets are not met with diet/metformin then insulin should be added

Important for me Less important

This patient fulfilled the criteria for a diagnosis of gestational diabetes on her original OGTT at 25 weeks, due to a fasting glucose > 5.6mmol/L. Her glycaemic control has been refractory to lifestyle modifications, and, most recently, the addition of metformin, as her fasting glucose has remained above 5.6mmol/L. At this stage, NICE advise that short-acting insulin should be added to her existing treatment.

Although the patient's fasting glucose has improved slightly with the addition of metformin, her fasting glucose reading is still above the target range. As such, it would not be appropriate to continue with her current treatment, and risk the fetal and maternal complications of gestational diabetes.

Changing metformin to modified-release metformin can be helpful in patients who do not tolerate metformin due to side-effects such as gastrointestinal upset, but would not have a role in improving glycaemic control in this patient.

NICE advise that in the instance of persistent impaired glycaemic control, insulin should be added in conjunction with metformin, rather than substituted for it.

Sulfonylureas such as glibenclamide should only be offered for patients who cannot tolerate metformin, or as an adjunct for patients who decline insulin treatment, and would not be the most appropriate next drug for this patient.

👍 👎 Discuss (5) Improve

Next question

Gestational diabetes ★

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:

- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes

- BMI of > 30 kg/m²
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2

- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

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Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

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Question 167 of 414 ✓

Which one of the following serum proteins is most likely to increase in a patient with severe pneumococcal pneumonia?

Transferrin	8%
Transthyretin	4%
Ferritin	74%
Albumin	3%
Cortisol binding protein	11%

The correct answer is **Ferritin**. Ferritin, a ubiquitous intracellular protein that stores iron and releases it in a controlled fashion, is known as an acute phase reactant. Acute phase reactants are proteins whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. During severe infections such as pneumococcal pneumonia, the body's inflammatory response leads to an increase in the production of certain proteins, including ferritin. The elevated levels of ferritin serve as a marker for systemic inflammation and infection.

Transferrin is incorrect because it is a negative acute-phase protein; its levels typically decrease during inflammation or infection. Transferrin is responsible for iron transport in the body. During an infection or inflammatory state, the liver produces more positive acute-phase proteins and fewer negative ones like transferrin.

Transthyretin, also known as prealbumin, serves as a transport protein for thyroxine and retinol-binding protein. It's often used as an indicator of nutritional status rather than inflammation or infection. Like transferrin, transthyretin is also considered a negative acute phase reactant and its level decreases during inflammation.

Albumin too falls under the category of negative acute-phase proteins which means its serum concentration decreases in response to systemic inflammation or infection. Albumin mainly functions to regulate the colloidal osmotic pressure of blood.

Lastly, **Cortisol binding protein**, also known as transcortin, binds cortisol and transports it around the body. Its levels do not significantly change during an inflammatory response or infection condition like pneumococcal pneumonia.

Therefore, out of all options provided, only ferritin would most likely increase in a patient with severe pneumococcal pneumonia due to its role as a positive acute phase reactant.

👍 👎 Discuss (1) Improve

Next question

Acute phase proteins ★

Acute phase proteins
- CRP*
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component**
- haptoglobin
- complement

During the acute phase response the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include:
- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

*Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesised in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

**plays a more significant role in other mammals such as mice

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Question 168 of 414 ✓

Whilst an inpatient for a chest infection, a 64-year-old man is reviewed by the hospital's diabetic specialist nurse. His diabetic control has generally been inadequate, despite trying a number of medications. The latest blood test shows his HbA1c to still be above the normal range. The diabetic specialist nurse decides to commence another medication and advises the GP to review with a repeat blood test in several months' time. The patient is warned about serious adverse effects - in particular, Fournier gangrene.

What is the mechanism of action of this drug?

Activates peroxisome proliferator-activated receptor-gamma	10%
Blocks ATP-sensitive potassium channels	5%
Activates glucagon-like peptide 1 receptors	7%
Inhibits sodium-glucose co-transporter 2	72%
Inhibits dipeptidyl peptidase-4	7%

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule

Important for me Less important

The correct answer is the inhibition of sodium-glucose co-transporter 2 (SGLT-2). SGLT-2 inhibitors include empagliflozin and dapagliflozin. Patients taking these drugs often lose weight, which may be beneficial. Key side effects include urinary/genital infections secondary to glycosuria and normoglycaemic ketoacidosis. There is a known serious adverse affect of this class of drugs causing Fournier gangrene.

Activation of peroxisome proliferator-activated receptor-gamma (PPAR gamma) refers to the thiazolidinedione class of drugs, including pioglitazone. The activated receptor complex affects a number of target genes which ultimately decrease insulin resistance and cause a number of other effects.

Blockage of ATP-sensitive potassium channels describes the action of sulfonylureas such as gliclazide. These may induce hypoglycaemia and are known to cause weight gain.

Activation of glucagon-like peptide 1 receptors refers to the aptly-named glucagon-like peptide 1 (GLP-1) mimetics, including exenatide. These are a relatively new class of drug and have the added beneficial effect of weight loss. They are much further down the order of use in diabetic guidelines and so are not widely seen in use.

Inhibition of dipeptidyl peptidase-4 (DPP4) is the method of action of the 'gliptin' drugs, including sitagliptin and linagliptin. They ultimately lead to increased levels of incretin circulation, similarly to GLP-1 mimetics.

👍 👎 Discuss (3) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

B *I* A T↕

Textbooks

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Question 169 of 414 ✗

A 55-year-old female is reviewed in the diabetes clinic. The following results are obtained:

Urinalysis	protein +
HbA1c	86 mmol/mol (10.0%)

What average blood glucose level for the past 2 months is this most likely to represent?

	9	5%
	10	17%
🟥	11	12%
🟩	15	42%
	There is no relation between HbA1c and average blood glucose	24%

Discuss (9) | Improve

Next question

Glycosylated haemoglobin ★

Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus. HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration. The level of HbA1c therefore is dependent on:

- red blood cell lifespan
- average blood glucose concentration

A number of conditions can interfere with accurate HbA1c interpretation:

Lower-than-expected levels of HbA1c (due to reduced red blood cell lifespan)	Higher-than-expected levels of HbA1c (due to increased red blood cell lifespan)
Sickle-cell anaemia GP6D deficiency Hereditary spherocytosis Haemodialysis	Vitamin B12/folic acid deficiency Iron-deficiency anaemia Splenectomy

HbA1c is generally thought to reflect the blood glucose over the previous '3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks. NICE recommend '*HbA1c should be checked every 3-6 months until stable, then 6 monthly*'.

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

HBA1c (%)	Average plasma glucose (mmol/l)	IFCC-HbA1c (mmol/mol)
5	5.5	
6	7.5	42
7	9.5	53
8	11.5	64
9	13.5	75
10	15.5	
11	17.5	
12	19.5	

From the above we can see that average plasma glucose = (2 * HbA1c) - 4.5

Next question

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Question 170 of 414 ✗

A 31-year-old woman presents for review. For the past few months she has been feeling generally tired and has not had a normal period for around 4 months. Prior to this she had a regular 30 day cycle. A pregnancy test is negative, pelvic examination is normal and routine bloods are ordered:

FBC	Normal
U&E	Normal
TFT	Normal
Follicle-stimulating hormone	41 iu/l (< 35 iu/l)
Luteinizing hormone	33 mIU/l (< 20 mIU/l)
Oestradiol	70 pmol/l (> 100 pmol/l)

What is the most likely diagnosis?

	Ovarian cancer	1%
	Gonadotropin-producing pituitary adenoma	18%
🟥	Turner syndrome	2%
🟩	Premature ovarian failure	75%
	Aromatase enzyme deficiency	4%

The correct answer is **premature ovarian failure**. This diagnosis is supported by the patient's clinical presentation of amenorrhea and fatigue, as well as the laboratory findings. The elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, along with the low oestradiol level, are indicative of a primary ovarian insufficiency. Premature ovarian failure occurs when a woman's ovaries stop producing eggs and hormones before the age of 40, leading to symptoms such as irregular or absent periods, hot flushes, and infertility.

Ovarian cancer is an unlikely diagnosis in this case because the patient's main presenting symptoms are fatigue and amenorrhea. While ovarian cancer can cause non-specific symptoms such as fatigue, it would not typically present with hormonal abnormalities like those seen in this patient.

Gonadotropin-producing pituitary adenoma is also an unlikely diagnosis because these tumours usually cause elevated FSH and LH levels alongside normal or high oestradiol levels. In addition, patients with pituitary adenomas often present with other signs and symptoms related to mass effect on surrounding structures, such as headaches or visual disturbances.

Turner syndrome is a genetic disorder that affects females who have only one X chromosome instead of two. It is associated with short stature, gonadal dysgenesis (leading to primary amenorrhea), and various other physical abnormalities. However, Turner syndrome would be diagnosed in childhood or adolescence rather than presenting for the first time at age 31.

Finally, **aromatase enzyme deficiency** is a rare genetic disorder that affects both males and females. Aromatase deficiency leads to impaired conversion of testosterone to oestradiol and increased circulating levels of testosterone. In females, this can result in ambiguous genitalia, lack of secondary sexual characteristics, and primary amenorrhea. However, this patient has a history of regular menstrual cycles prior to the onset of her current symptoms, which makes aromatase enzyme deficiency an unlikely diagnosis.

👍 👎 Discuss (2) Improve

Next question

Premature ovarian insufficiency ★

Premature ovarian insufficiency is defined as the onset of menopausal symptoms and elevated gonadotrophin levels before the age of 40 years. It occurs in around 1 in 100 women.

Causes of premature menopause include:
- idiopathic
  - the most common cause
  - there may be a family history
- bilateral oophorectomy
  - having a hysterectomy with preservation of the ovaries has also been shown to advance the age of menopause
- radiotherapy
- chemotherapy
- infection: e.g. mumps
- autoimmune disorders
- resistant ovary syndrome: due to FSH receptor abnormalities

Features are similar to those of the normal climacteric but the actual presenting problem may differ

- climacteric symptoms: hot flushes, night sweats
- infertility
- secondary amenorrhoea
- raised FSH, LH levels
  - e.g. FSH > 30 IU/L
  - elevated FSH levels should be demonstrated on 2 blood samples taken 4-6 weeks apart
- low oestradiol
  - e.g. < 100 pmol/l

Management

- hormone replacement therapy (HRT) or a combined oral contraceptive pill should be offered to women until the age of the average menopause (51 years)
  - it should be noted that HRT does not provide contraception, in case spontaneous ovarian activity resumes

Next question

B *I* A T↕

Textbooks

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Extended textbook

Links

Guys & St Thomas NHS 👍 0 👎 1

Premature ovarian failure information sheet

NICE 👍 0 👎 1

Diagnosing premature menopause

PassMedicine

Question 171 of 414 ✗

A 68-year-old woman is found to have the following blood tests:

TSH	0.05 mu/l
Free T4	19 pmol/l (range 9-25 pmol/l)
Free T3	7 pmol/l (range 3-9 pmol/l)

If left untreated, what are the most likely possible consequences?

🟩	Supraventricular arrhythmias and osteoporosis	53%
	Supraventricular arrhythmias and hyperlipidaemia	15%
🟥	Hypothyroidism and impaired glucose tolerance	19%
	Myasthenia gravis and hypothyroidism	3%
	Impaired glucose tolerance and hyperlipidaemia	10%

The correct answer is **Supraventricular arrhythmias and osteoporosis**. The patient's blood tests show low TSH and normal/high levels of Free T4 and Free T3, which are indicative of subclinical hyperthyroidism. If left untreated, this condition can lead to several complications. Supraventricular arrhythmias, such as atrial fibrillation, are a common cardiovascular complication of hyperthyroidism due to increased cardiac output and heart rate. Osteoporosis can also occur as a result of increased bone turnover caused by excess thyroid hormones.

The option **Supraventricular arrhythmias and hyperlipidaemia** is incorrect because hyperthyroidism typically leads to decreased lipid levels due to increased metabolism, not hyperlipidaemia.

Hypothyroidism and impaired glucose tolerance is also incorrect. The patient's test results indicate subclinical hyperthyroidism, not hypothyroidism. Furthermore, it's generally associated with improved glucose tolerance due to an increase in the rate of absorption of sugars from the gut and an increase in insulin clearance.

The choice **Myasthenia gravis and hypothyroidism** is incorrect as well. While thyroid diseases may be associated with myasthenia gravis (an autoimmune disorder), this is not a direct consequence of untreated subclinical hyperthyroidism.

Finally, the option **Impaired glucose tolerance and hyperlipidaemia** is incorrect for the reasons stated above: Hyperthyroidism typically improves glucose tolerance due to faster absorption rates from the gut and increases insulin clearance; it also tends to decrease lipid levels rather than causing hyperlipidaemia.

👍 👎 Discuss (3) Improve

Next question

Subclinical hyperthyroidism ★

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. It is defined as:
- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually < 0.1 mu/l)

Causes
- multinodular goitre, particularly in elderly females
- excessive thyroxine may give a similar biochemical picture

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (atrial fibrillation) and bone metabolism (osteoporosis). It may also impact on quality of life and increase the likelihood of dementia

Management
- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention
- a reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission

Next question

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Question 172 of 414 ✗

A 63-year-old woman presents to the emergency department with new-onset confusion.

Clinically, she appears well. Her chest is clear, capillary refill is less than 2 seconds, heart rate 65/min, alert, temperature 37.2 °C, no peripheral oedema.

Blood tests are ordered and results are as follows:

Na^+	121 mmol/L	(135 - 145)
K^+	4.1 mmol/L	(3.5 - 5.0)
Bicarbonate	24 mmol/L	(22 - 29)
Urea	5.1 mmol/L	(2.0 - 7.0)
Creatinine	103 µmol/L	(55 - 120)

Thyroid-stimulating hormone (TSH)	2.3 mU/L	(0.5-5.5)
Free thyroxine (T4)	14 pmol/L	(9.0 - 18.0)

Lithium level	0.8mmol/L	(0.4-1.0mmol/L)

Her past medical history includes depression, type II diabetes mellitus and hyperthyroidism. Her regular medications are atorvastatin, lithium, carbimazole, lofepramine and metformin.

Which of her medications is most likely to be the cause of her new-onset confusion?

	Atorvastatin	2%
🟥	Carbimazole	23%
	Lithium	38%
🟩	Lofepramine	34%
	Metformin	2%

SIADH - drug causes: carbamazepine, sulfonylureas, SSRIs, tricyclics

Important for me Less important

This woman is presenting with euvolaemic hyponatraemia caused by syndrome of inappropriate anti-diuretic hormone secretion (SIADH). As a tricyclic antidepressant, lofepramine is the only medication listed that can cause SIADH.

Atorvastatin has no effect on sodium levels and is not known on its own to cause confusion.

Lithium is a cause of diabetes insipidus, not SIADH. The lithium level is also within normal range and is hence unlikely to cause confusion.

Hypothyroidism can cause euvolaemic hyponatraemia, however, the thyroid function tests are within the normal range.

Sulfonylureas, not metformin, can cause SIADH.

👍 👎 Discuss (7) Improve

Next question

Syndrome of inappropriate ADH secretion ★

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention. Patients with SIADH are typically euvolemic, i.e. they do not show signs of overt volume depletion or overload.

Pathophysiology

- SIADH involves an excessive release of antidiuretic hormone (ADH), also known as vasopressin, which leads to water retention, volume expansion, and dilutional hyponatraemia
- ADH is produced by the hypothalamus and stored in the posterior pituitary gland. Its primary function is to regulate the body's water balance
- It does this by increasing water reabsorption in the collecting ducts of the kidneys, thereby decreasing the volume of urine produced
- In SIADH, there is an inappropriate and continuous release of ADH that is not inhibited by normal physiological mechanisms, such as adequate or excess body fluid levels
- As a result, the kidneys reabsorb more water, leading to decreased urine output, and expansion of extracellular fluid volume.
- Importantly, this increase in body fluid volume does not lead to the expected signs of fluid overload, such as oedema or hypertension, because the excess fluid is uniformly distributed

throughout all body fluid compartments.
- However, as water is retained in the body, the concentration of electrolytes in the blood, particularly sodium, becomes diluted, leading to hyponatraemia.

Causes of SIADH

Category	**Examples**
Malignancy	• **small cell lung cancer** • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• sulfonylureas* • SSRIs, tricyclics • carbamazepine • vincristine • cyclophosphamide
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias

Investigations
- Urine osmolality: Urine osmolality is inappropriately high (>100 mOsm/kg) in relation to serum osmolality, as the kidneys should normally dilute urine in the setting of low serum osmolality.
- Urine sodium concentration: Urine sodium concentration is typically high (>40 mmol/L) due to the action of ADH on the renal tubules.

Management
- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction

- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

Next question

Textbooks

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Extended textbook

Media

WHAT IS...
SIADH?

Syndrome of inappropriate antidiuretic hormone (SIADH)

Osmosis - YouTube 👍 31 👎 0

Report broken media

Score: **23.8%**

1 ✓
2 ✓
3 ✓

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Question 173 of 414 ✗

A 57-year-old woman is referred to urogynaecology with symptoms of urge incontinence. A trial of bladder retraining is unsuccessful. It is therefore decided to use a muscarinic antagonist.

Which one of the following medications is an example of a muscarinic antagonist?

Tolterodine	76%
Teriparatide	5%
Toremifene	4%
Finasteride	6%
Tamsulosin	9%

Other examples of muscarinic antagonists used in urinary incontinence include oxybutynin and solifenacin. Examples of muscarinic antagonists used in different conditions include ipratropium (chronic obstructive pulmonary disease) and procyclidine (Parkinson's disease).

Tamsulosin is an alpha blocker.

Discuss Improve

Next question

Urinary incontinence

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index

- hysterectomy
- family history

Classification

- overactive bladder (OAB)/urge incontinence
    - due to detrusor overactivity
    - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
    - comorbid physical conditions impair the patient's ability to get to a bathroom in time
    - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
    - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
    - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
    - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures

- a combined noradrenaline and serotonin reuptake inhibitor
- mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

Report broken link

Media

URINARY INCONTINENCE

Urinary incontinence

Osmosis - YouTube 👍 0 👎 1

Report broken media

PassMedicine

Question 174 of 414 ✕

A 53 year man presents as his wife has noticed a change in his appearance. He has also noticed his hands seem larger. On examination blood pressure is 170/94 and he is noted to have bitemporal hemianopia. What is the most appropriate first-line treatment?

	Octreotide	32%
	External irradiation	0%
🟥	Pegvisomant	5%
🟩	Trans-sphenoidal surgery	54%
	Bromocriptine	9%

Trans-sphenoidal surgery is the treatment of choice in acromegaly. There is no significant evidence base supporting the use of pre-operative octreotide

Discuss (10) | Improve

Next question

Acromegaly: management ★

Trans-sphenoidal surgery is the first-line treatment for acromegaly in the majority of patients.

If a pituitary tumour is inoperable or surgery unsuccessful then medication may be indicated:

- somatostatin analogue
  - directly inhibits the release of growth hormone
  - for example octreotide
  - effective in 50-70% of patients
- pegvisomant
  - GH receptor antagonist - prevents dimerization of the GH receptor
  - once daily s/c administration
  - very effective - decreases IGF-1 levels in 90% of patients to normal

  - doesn't reduce tumour volume therefore surgery still needed if mass effect
- dopamine agonists
  - for example bromocriptine
  - the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
  - effective only in a minority of patients

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Postgraduate Medical Journal 7 2

Modern treatment of acromegaly

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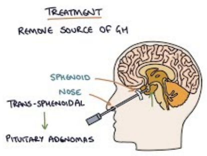
Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube

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Question 175 of 414 ✗

A 51-year-old woman has recently been diagnosed with a renal calculus following a CT scan after presenting to hospital with loin pain. Her blood results are shown below:

Calcium	2.85 mmol/L	(2.1-2.6)
Phosphate	0.72 mmol/L	(0.8-1.4)
Parathyroid hormone	7.0 pmol/L	(1.6-6.9)
Vitamin D	85 nmol/L	(50-250)
Creatinine	76 µmol/L	(55 - 120)

Her 24-hour urinary calcium excretion and dual-energy X-ray absorptiometry (DEXA) results are both normal.

She has no other symptoms and no other medical problems.

What would be the most appropriate definitive management strategy for her condition?

🟥	Commence bisphosphonate	6%
	Commence cinacalcet	10%
	Intravenous fluids	14%
	Observe with regular serum calcium and PTH measurements	9%
🟩	Referral for parathyroid surgery	61%

The definitive management of primary hyperparathyroidism is total parathyroidectomy

Important for me Less important

This patient has symptoms and biochemical findings compatible with primary hyperparathyroidism.

Current NICE guidance recommends referral for consideration of parathyroid surgery if a patient has one or more of the following:

- Symptoms of hypercalcaemia (e.g. thirst, polyuria, constipation)

- End-organ disease (renal calculi, fragility fractures or osteoporosis)
- Corrected serum calcium of 2.85 mmol/L or above

As she has renal calculi, the broad consensus is that surgery is beneficial as it is curative of the underlying condition, relieves symptoms and can prevent future adverse events.

Calcimimetics can be considered in some patients who decline or are unsuitable for surgery.

Bisphosphonates can be considered in patients with primary hyperparathyroidism who have a high fracture risk.

Intravenous fluids are not necessary for mild or moderate hypercalcaemia.

Discuss (3) Improve

Next question

Primary hyperparathyroidism

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':
- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture

- renal stones
- hypertension

Associations

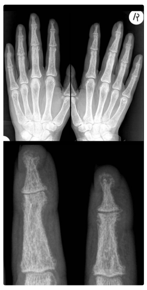
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- bloods
    - raised calcium, low phosphate
    - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
    - pepperpot skull
    - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



Next question

PassMedicine

Question 176 of 414 ✗

A 28-year-old female is brought in by her parents following a mixed overdose. They report the patient had locked herself in her room following an argument. As the patient has a history of depression and previous suicide attempts, after a short period of time they forced open her door and found her drowsy on the floor. They also found her grandmother's medical box, containing paracetamol, gliclazide, bisoprolol and atorvastatin empty but they do not know how much of each she has ingested.

On examination, the patient is sweaty with a global tremor and is confused. She is tachycardic and seems globally weak.

Which of the following molecules is likely to be first produced by the patient in response to their overdose?

	Glycogen synthase	4%
	Cortisol	15%
🟩	Glucagon	69%
🟥	Glutathione	7%
	Glycogen phosphorylase	5%

Glucagon is the first hormone secreted in response to hypoglycaemia

Important for me Less important

The most likely overdose presentation, in this case, is that of hypoglycaemia secondary to gliclazide ingestion. The patient has the typical sign of hypoglycaemia with acute onset sweating, weakness and confusion. None of the other potential medications ingested would produce the patient's clinical picture. In hypoglycaemia, the first response of the body is to decrease the production of insulin and then to increase glucagon secretion. Glucagon promotes gluconeogenesis in an attempt to raise blood glucose levels.

Glycogen synthase is one of the main enzymes involved in glycogenesis which is the conversion of glucose into the body storage component glycogen. As this patient has most likely suffered a hypoglycaemic event secondary to gliclazide ingestion gluconeogenesis to release glucose and not glycogenesis is carried out by the body.

Cortisol is released in hypoglycaemia however it is a later response and is secreted well after glucagon. Cortisol is a steroid hormone in the glucocorticoid class that also promotes gluconeogenesis and therefore glucose production.

Glutathione is an antioxidant found in the liver which is involved in the neutralisation and excretion of the toxic paracetamol metabolite N-acetyl-p-benzoquinone imine (NAPQI). In paracetamol overdose, glutathione levels are depleted. Glutathione levels are replenished by the antidote treatment acetylcysteine. This patient presentation is not in keeping with paracetamol overdose as her symptoms are too acute onset. Paracetamol overdose results in liver failure however this takes several hours to develop and even longer before physical symptoms occur.

Glycogen phosphorylase is one of the key enzymes involved in glycogenolysis, which is the breakdown of glycogen. It is a phosphorylase enzyme and catalyzes the rate-limiting step in glycogenolysis, therefore, its production is increased in response to hypoglycaemia however this increase is regulated by glucagon i.e. glucagon increases first which then brings about an increase in glycogen phosphorylase.

👍 👎 Discuss (3) Improve

Next question

Hypoglycaemia ★

Causes
- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
    - causes exaggerated insulin secretion
    - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia
- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but

later

- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
    - Sweating
    - Shaking
    - Hunger
    - Anxiety
    - Nausea
- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
    - Weakness
    - Vision changes
    - Confusion
    - Dizziness
- Severe and uncommon features of hypoglycaemia include:
    - Convulsion
    - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):
    - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
    - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
    - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
    - If the patient is alert, a quick-acting carbohydrate may be given (as above)
    - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
    - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

PassMedicine

Question 177 of 414 ✗

A 17-year-old girl presents with a 6 week history of nausea and abdominal discomfort. Routine blood tests reveal the following.

Hb	10.9 g/dl
WBC	6.7 *10^9/l
Platelets	346 *10^9/l
Calcium	2.33 mmol/l
Bilirubin	7 μmol/l
ALP	262 u/l
ALT	35 u/l

What is the most likely diagnosis?

Alcoholic liver disease	3%
Cholangiocarcinoma	4%
🟩 Pregnancy	52%
🟥 Gallstones	22%
Primary biliary cirrhosis	20%

Alkaline phosphatase is significantly elevated in pregnancy. This would also explain the borderline anaemia

Discuss (11) Improve

Next question

Alkaline phosphatase

Causes of raised alkaline phosphatase (ALP)

- liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- osteomalacia
- bone metastases
- hyperparathyroidism
- renal failure
- physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level

Raised ALP and raised calcium	**Raised ALP and low calcium**
Bone metastases Hyperparathyroidism	Osteomalacia Renal failure

Next question

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Score: **23.2%**

1 ✓

2 ✓

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← Question 178 of 414 ✓ ⚐ →

A 15-year-old girl is investigated for primary amenorrhoea, despite having developed secondary sexual characteristics at 11 years of age. On examination she has well developed breasts with scanty pubic hair and small bilateral groin swellings. What is the most likely diagnosis?

Congenital adrenal hyperplasia	21%
Polycystic ovarian syndrome	3%
Turner's syndrome	16%
[✓ Complete androgen insensitivity syndrome]	47%
Mullerian duct agenesis	12%

The correct answer in this case is **Complete androgen insensitivity syndrome** (CAIS). This condition occurs when an individual with XY chromosomes and testes develops as a phenotypic female due to a complete inability of the body's cells to respond to androgens. In CAIS, individuals typically have normal female external genitalia, well-developed breasts, scanty or absent pubic hair, and no menstruation due to the absence of uterus and fallopian tubes. The small bilateral groin swellings are likely to be undescended testes.

Congenital adrenal hyperplasia is an incorrect answer because it is a group of inherited disorders affecting the adrenal glands, leading to an impaired production of cortisol and often aldosterone. This results in an overproduction of androgens which can cause ambiguous genitalia in females at birth or virilisation during childhood or adolescence. Primary amenorrhoea could occur in severe cases; however, the presence of well-developed breasts and scanty pubic hair is not consistent with this diagnosis.

Polycystic ovarian syndrome (PCOS) is also an incorrect answer. PCOS is characterised by menstrual irregularities, hyperandrogenism, and polycystic ovaries on ultrasound. Although primary amenorrhoea may occur in some cases, it would be unusual for a patient with PCOS to have well-developed breasts without significant pubic hair growth due to increased levels of circulating androgens.

Turner's syndrome is another incorrect option. Turner's syndrome occurs when there is complete or partial absence of one X chromosome in females (45,XO karyotype), resulting in short stature, gonadal dysgenesis with streak ovaries, webbed neck, low-set ears, widely spaced nipples, lymphoedema at birth and cubitus valgus. Primary amenorrhoea is a common feature; however, the well-developed breasts and small bilateral groin swellings are not consistent with this diagnosis.

Finally, **Mullerian duct agenesis**, also known as Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, is an incorrect answer. This condition is characterised by congenital absence or underdevelopment of the uterus and upper two-thirds of the vagina in females with normal 46,XX karyotype and ovarian function. Although primary amenorrhoea would be expected in these individuals, they would typically have normal secondary sexual characteristics including pubic hair growth, which is inconsistent with the clinical presentation described in the question.

Discuss (5) Improve

Next question

Androgen insensitivity syndrome

Androgen insensitivity syndrome is an X-linked recessive condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- 'primary amenorrhoea'
- little or no axillary and pubic hair
- undescended testes causing groin swellings
- breast development may occur as a result of the conversion of testosterone to oestradiol

Diagnosis

- buccal smear or chromosomal analysis to reveal 46XY genotype
- after puberty, testosterone concentrations are in the high-normal to slightly elevated reference range for postpubertal boys

Management

- counselling - raise the child as female
- bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- oestrogen therapy

Next question

PassMedicine

Question 179 of 414 ✗

A woman presents to her GP with increased pelvic pain, vaginal discharge, and post-coital bleeding. On questioning, she reports loss of appetite and unintentional weight loss. She is referred to the hospital for a colposcopy where abnormal cells are detected.

Considering the likely diagnosis, which of these is the most important risk factor?

	Being nulliparous	4%
🟩	Smoking	60%
	Having the genetic mutation BRCA1 or BRCA2	5%
	Detection of human papillomavirus (HPV) strains HPV-6 or HPV-11	28%
🟥	Being above 45 years old	2%

Women who smoke are at a two-fold increased risk of developing cervical cancer than women who do not

Important for me Less important

This woman likely has cervical cancer.

Women who smoke are at two-fold increased risk of developing cervical cancer than women who do not, therefore smoking is the correct answer.

Being nulliparous is not the correct answer as it does not increase the risk of cervical cancer. It is thought to be a risk factor for ovarian cancer. Conversely, having three or more children is a risk factor for cervical cancer.

BRCA1 and BRCA2 are tumour suppressor genes. They are implicated in breast and ovarian cancers, but not cervical cancer.

HPV is the largest risk factor for cervical cancer. However, the strains HPV-6 and HPV-11 are low-risk strands which cause warts but are unlikely to cause cervical cancer.

Being above 45 years old is incorrect. The risk of cervical cancer is highest in people aged 25-29 years. Around 50% of cases of cervical cancer occur in women under the age of 45 years.

👍 👎 Discuss (5) Improve

Next question

Cervical cancer ★

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. It may be divided into:

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papillomavirus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov 10;370(9599):1609-21) confirmed the link

Next question

Textbooks

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Links

Cancer Research UK 👍 0 👎 0

Cervical cancer

Clinical Knowledge Summaries 👍 0 👎 3

Cervical cancer management guidelines

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Media

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Cervical Cancer
Medical Student Review

Cervical cancer

Osmosis - YouTube 👍 6 👎 3

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Score: **23.5%**

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Question 180 of 414 ✓

Which of the following is least recognised as a potential complication of acromegaly?

Colorectal cancer	27%
Hypertension	4%
Cardiomyopathy	6%
Diabetes mellitus	7%
Pulmonary hypertension	57%

Acromegaly is associated with systemic rather than pulmonary hypertension.

Secondary causes of pulmonary hypertension include COPD, congenital heart disease (Eisenmenger's syndrome), recurrent pulmonary embolism, HIV and sarcoidosis.

Discuss (3) Improve

Next question

Acromegaly: features

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic.

Features
- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin: caused by sweat gland hypertrophy
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea
- 6% of patients have MEN-1

Complications

- hypertension
- diabetes (>10%)
- cardiomyopathy
- colorectal cancer

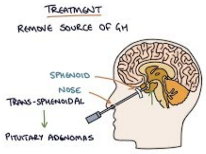
Next question

Textbooks

High-yield textbook

Extended textbook

Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

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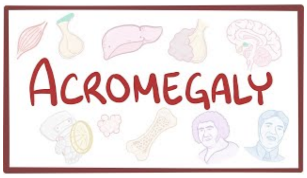
ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 12 👎 1

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Question 181 of 414 ✗

A 30-year-old female presented to the GP surgery for a cervical smear as part of routine cervical cancer screening. She has been married for 2 years with no offspring. She drinks 30 units of alcohol weekly and smokes 15 cigarettes per day for 10 years.

The smear result revealed an abnormal finding and subsequent colposcopy and biopsy revealed a diagnosis of cervical squamous cell carcinoma.

Which of the following aspect of the patient's history is the most significant risk factor for developing this condition?

	Age	1%
🟥	Alcohol	1%
🟩	Cigarette smoking	67%
	Nulliparity	9%
	Human papillomavirus (HPV) type 11	22%

Women who smoke are at a two-fold increased risk of developing cervical cancer than women who do not

Important for me Less important

Human papillomavirus (HPV), particularly serotypes 16,18 and 33, is by far the most important factor in the development of cervical cancer. Other risk factors include smoking, human immunodeficiency virus, early first intercourse, many sexual partners, high parity, lower socioeconomic status and the use of the combined oral contraceptive pill.

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, however, this is not the most significant risk factor.

Alcohol intake and nulliparity are associated with increased risk of developing breast cancer, but not cervical cancer. In fact, cervical cancer risk is 15% higher in women who have had 1 full-term pregnancy compared with those who have had none.

HPV type 11 is a cause of benign genital warts.

Discuss (1) Improve

Next question

Cervical cancer

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. It may be divided into:

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papillomavirus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
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Next question

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Cervical cancer

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Cervical cancer management guidelines

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Score: **23.8%**

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Question 182 of 414 ✗

A 21-year-old man presents to his general practitioner with polydipsia and polyuria. He has no significant past medical history and is not on any regular medications. His father developed diabetes at aged 20. He does not smoke or drink alcohol.

The examination is unremarkable. His body mass index is 22 kg/m^2. His hearing and vision are normal.

Blood tests:

Hb	138 g/L	Male: (135-180) Female: (115 - 160)
Platelets	189 * 10^9/L	(150 - 400)
WBC	4.9 * 10^9/L	(4.0 - 11.0)
Na$^+$	136 mmol/L	(135 - 145)
K$^+$	4.2 mmol/L	(3.5 - 5.0)
Urea	5.2 mmol/L	(2.0 - 7.0)
Creatinine	89 µmol/L	(55 - 120)
CRP	4 mg/L	(< 5)
HbA1c	74 mmol/L	(<42)
Calcium	2.24 mmol/L	(2.2-2.6)

Further testing:

Anti-islet cell antibodies	negative
Anti - GAD antibodies	negative
Anti - insulin antibodies	negative

Given the likely diagnosis, what is the typical inheritance pattern of this condition?

Autosomal dominant	72%
Autosomal recessive	9%

Polygenic	13%
Mitochondrial	2%
X-linked recessive	4%

MODY is inherited in an autosomal dominant fashion so a family history is often present

Important for me Less important

Autosomal dominant is the correct answer. The patient presents with polydipsia and polyuria with a very elevated HbA1c. He is of normal weight and his diabetes autoantibodies are negative, making traditional type 1 and type 2 diabetes less likely. The family history of his father developing diabetes at 20 should raise suspicion of mature onset diabetes of youth (MODY). This is a monogenic disorder, typically inherited in an autosomal dominant fashion.

Polygenic is incorrect. Traditional forms of type 1 and type 2 diabetes are polygenic rather than monogenic. This means they are related to a change or defect in multiple genes, rather than one alone.

Autosomal recessive is incorrect. Neonatal diabetes mellitus can is a monogenic form of diabetes that occurs in the first 6-12 months of life. The onset is too late here. Wolfram syndrome (DIDMOAD) can also cause diabetes mellitus (along with diabetes insipidus, optic atrophy and deafness). The absence of visual or hearing problems makes this less likely.

Mitochondrial is incorrect. Patients with maternally inherited diabetes and deafness inherit the disorder via mitochondrial inheritance. The absence of sensorineural hearing loss, in this case, points away from this disorder.

X-linked recessive is incorrect. Some forms of diabetes insipidus can be inherited in this pattern but the more likely diagnosis, in this case, is a form of diabetes mellitus.

👍 👎 Discuss (2) Improve

Next question

MODY

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

Textbooks

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Score: **23.6%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗

PassMedicine

Question 183 of 414 ✗

A patient diagnosed with chronic primary hyperparathyroidism was treated by parathyroidectomy and you are seeing him in clinic as a follow-up. His post-operative bloods are available to you in clinic:

Parathyroid hormone	1.8 pmol/L (1.6 - 6.9 pmol/L)
Corrected calcium	1.7 mmol/L (2.1 - 2.6 mmol/L)
Phosphate	0.1 mmol/L (0.1 - 0.8 mmol/L)

What is the most likely explanation for this?

	Osteomalacia	19%
🟩	Hungry bone syndrome	69%
🟥	Rickets	2%
	Scurvy	1%
	Parathyroid adenoma	9%

Hungry bone syndrome is the result of a sudden drop in previously high parathyroid hormone levels

Important for me Less important

This question tests your knowledge of the complications of a parathyroidectomy following chronic hyperparathyroidism.

Osteomalacia - this is not the correct answer. Osteomalacia is a chronic condition which is not consistent with this patient's history.

Hungry bone syndrome - this is the correct answer. This presentation is a typical presentation of hungry bone syndrome, a rare but significant condition following a parathyroidectomy following chronic hyperparathyroidism. It causes hypocalcaemia.

Rickets - this is not the correct answer. Rickets is a condition in children.

Scurvy - this is not the correct answer. Scurvy is a vitamin deficiency which would not cause this picture.

Parathyroid adenoma - this is not the correct answer. This is more likely to cause hypercalcaemia.

Discuss (4) Improve

Next question

Hungry bone syndrome

Hungry bone syndrome is an uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long-standing. The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones. This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated. Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half-life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'. This process can be uncomfortable and also result in systemic hypocalcaemia.

Next question

Textbooks

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Question 184 of 414 ✓

A 66-year-old man attends clinic for review of his diabetic control. He has a history of type 2 diabetes mellitus, and was commenced on metformin six months' ago. The patient's HbA1c today is 60mmol/mol. You discuss the patient with your consultant, who recommends addition of empagliflozin for glycaemic control.

What is the mechanism of action of this medication?

Biguanide	1%
Sulfonylurea	2%
GLP-1 mimetic	3%
SGLT-2 inhibitor	90%
DPP-4 inhibitor	5%

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule

Important for me Less important

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule. In doing so, they reduce glucose reabsorption and increase urinary glucose excretion. This mechanism explains their main side effects - increased urine output, weight loss and urinary infections. Examples include canagliflozin, dapagliflozin and empagliflozin.

SGLT-2 inhibitors are often the best option in patients with ischaemic heart disease and heart failure who have not achieved adequate glycaemic control on metformin alone.

Important adverse effects include:

- Urinary and genital infection (secondary to glycosuria).
- Normoglycaemic ketoacidosis
- Increased risk of lower-limb amputation: feet should be closely monitored

Biguanides (such as metformin) act to decrease gluconeogenesis in the liver and increase insulin sensitivity.

Sulfonylureas (such as gliclazide) act to increase insulin release from beta-cells in the pancreas.

GLP-1 mimetics (such as exenatide) mimic incretin which is usually released in the gastrointestinal tract, and has the effect of increasing insulin production.

DPP-4 inhibitors (such as sitagliptin) act to block the action of DPP-4, an enzyme which breaks down incretin.

Discuss (3) Improve

Next question

SGLT-2 inhibitors

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

B I A

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Question 185 of 414 ✓

Each one of the following is associated with pseudohypoparathyroidism, except:

Low calcium levels	15%
[✓ Low PTH levels]	56%
Shortened 4th and 5th metacarpals	11%
Low IQ	12%
Short stature	5%

Discuss (1) Improve

Next question

Hypoparathyroidism

Primary hypoparathyroidism
- decrease PTH secretion
- e.g. secondary to thyroid surgery*
- low calcium, high phosphate
- treated with alfacalcidol

The main symptoms of hypoparathyroidism are secondary to hypocalcaemia:
- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- Trousseau's sign: carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- Chvostek's sign: tapping over parotid causes facial muscles to twitch
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Pseudohypoparathyroidism

- target cells being insensitive to PTH
- due to abnormality in a G protein
- associated with low IQ, short stature, shortened 4th and 5th metacarpals
- low calcium, high phosphate, high PTH
- diagnosis is made by measuring urinary cAMP and phosphate levels following an infusion of PTH. In hypoparathyroidism this will cause an increase in both cAMP and phosphate levels. In pseudohypoparathyroidism type I neither cAMP nor phosphate levels are increased whilst in pseudohypoparathyroidism type II only cAMP rises.

Pseudopseudohypoparathyroidism

- similar phenotype to pseudohypoparathyroidism but normal biochemistry

*this may seem an oxymoron, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism'

Next question

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Score: **24.3%**

1 ✓
2 ✓

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Question 186 of 414 ✗

A 64-year-old woman presents with increased breathlessness. Her medical history includes COPD. She started a rescue pack of prednisolone 40mg OD three days ago. She is afebrile, respiratory rate of 29/min, a heart rate of 79bpm, oxygen saturation of 85% on room air. Her chest x-ray shows no acute lung pathology. Salbutamol nebulisers and oxygen via venturi mask are started. Four hours later, she is euvolemic and afebrile, her RR is 22/min, HR 98bpm, and oxygen saturations are 88% on room air. Her blood results show:

WBC	15.4 * 10^9/L	(4.0 - 11.0)
Urea	9.9 mmol/L	(2.0 - 7.0)
Creatinine	85 µmol/L	(55 - 120)
CRP	4 mg/L	(< 5)

What would you do next?

🟩	Continue with current management plan	47%
🟥	Increase prednisolone dose	13%
	Start IV crystalloid fluids	10%
	Start amoxicillin PO	10%
	Take blood cultures and start co-amoxiclav IV	20%

Corticosteroids can induce neutrophilia

Important for me Less important

The patient's vital signs remain abnormal but have improved from admission. Consideration for sepsis or severe inflammatory response syndrome is a valid concern. However, overall there has been a clinical improvement with initial management. Therefore, **continuing with the current management plan** is valid. Beta agonism from the salbutamol nebulisers can explain the mild tachycardia. The raised WBC can be accounted for by the steroids inducing neutrophilia by inhibiting neutrophil apoptosis and releasing neutrophils that have adhered to vascular endothelial lining. Given the lack of pyrexia, the clear chest x-ray, and the normal CRP, a bacterial infective process is likely not present.

Increasing the dose of prednisolone will not speed up recovery in this case and will increase the risk of developing corticosteroid side effects. Patients with COPD should have availability to a 'rescue pack' of prednisolone to avoid unnecessary hospital presentation ls of exacerbation of COPD. Oral administration of steroids is the preferred route as they have the same bioavailability as IV steroids.

Starting IV crystalloid fluids is not required as the increase in urea is unlikely secondary to hypovolemia, given the patient's fluid status. Corticosteroids and protein catabolism should be considered a cause of an isolated raised urea when renal dysfunction is not present. Inappropriate IV fluids may cause iatrogenic fluid overload.

Starting amoxicillin PO will not be helpful as an infective process is not present and raises the risk of promoting antibiotic-resistant bacteria. Most COPD exacerbations are viral in aetiology. Symptoms such as sputum colour changes, increased sputum volume or thickness, or pyrexia could indicate a bacterial cause.

Taking blood cultures and starting co-amoxiclav IV is not indicated as there is no indication to take blood cultures and co-amoxiclav would not be the first-line antibiotic for a patient with an infective exacerbation of COPD unless previous microbiological investigations found specific bacteria susceptible to co-amoxiclav. Starting antibiotics inappropriately may lead to antibiotics-associated complications such as *Clostridium difficile* infection. Oral antibiotics have similar bioavailability to IV antibiotics of the same class and should be preferred unless stated otherwise.

Discuss (6) Improve

Next question

Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	**Glucocorticoid activity, high mineralocorticoid activity,**	**Predominant glucocorticoid activity, low mineralocorticoid activity**	**Very high glucocorticoid activity, minimal mineralocorticoid activity**
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

The side effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects
- endocrine
  - impaired glucose regulation
  - increased appetite/weight gain
  - hirsutism
  - hyperlipidaemia
- Cushing's syndrome
  - moon face
  - buffalo hump
  - striae
- musculoskeletal
  - osteoporosis
  - proximal myopathy
  - avascular necrosis of the femoral head
- immunosuppression
  - increased susceptibility to severe infection
  - reactivation of tuberculosis
- psychiatric
  - insomnia
  - mania
  - depression
  - psychosis
- gastrointestinal
  - peptic ulceration
  - acute pancreatitis
- ophthalmic
  - glaucoma
  - cataracts

- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
- longer-term systemic corticosteroids suppress the natural production of endogenous steroids. They should therefore not be withdrawn abruptly, as this may precipitate an Addisonian crisis
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have:
    - received more than 40mg prednisolone daily for more than one week
    - received more than 3 weeks of treatment
    - recently received repeated courses

Next question

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Score: **24.2%**

1 ✓
2 ✓

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← Question 187 of 414 ✗ →

A 60-year-old female, who is a known type 2 diabetic, presents to the GP for a diabetes review. She is already on metformin and her GP decided to start her on a sulphonylurea to help gain better control of her blood sugar. What is the mechanism of action of this medication?

	Closes calcium channels on the beta cells	1%
	Opens calcium channels on the beta cells	4%
	Inhibits sodium transport in the beta cells	4%
🟥	Opens potassium-ATP channels on the beta cells	56%
🟩	Closes potassium-ATP channels on the beta cells	35%

Sulfonylureas - bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells

Important for me Less important

Sulphonylureas work via mimicking the role of ATP on potassium-ATP channels from the outside. They act to block these channels causing membrane depolarisation and thus opening of voltage-gated calcium channels. This process results in the stimulation of insulin release.

When used acutely they increase insulin secretion and decrease insulin clearance in the liver. However, due to this stimulation of insulin secretion they can cause hypoglycaemia, the main side effect, and this can lead to the serious complication of neuroglycopenia.

This resulting lack of glucose supply to the brain can cause confusion and possible coma. Treatment of this should be through oral glucose, intramuscular glucagon or intravenous glucose.

If the tissue is exposed chronically to sulphonylureas there is no acute increase in insulin release but a decrease in plasma glucose concentration does remain. Chronic exposure to sulphonylureas does also lead to down-regulation of their receptors.

Discuss (6) Improve

Next question

Sulfonylureas ★

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

Textbooks

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Question 188 of 414 ✓

A 78-year-old woman with a background of severe chronic obstructive pulmonary disease (COPD) reports episodes of urinary incontinence, which she finds distressing. She has a chronic cough and reports that during more intense coughing episodes she passes a small amount of urine. She also reports that when her bladder feels full she can pass urine on the way to the toilet as she cannot get there quickly enough.

The GP initially prescribed her some pelvic floor exercises, but they did not make a difference as she was too breathless to complete them. The patient stated that she does not want any operations as she is afraid that she would not survive the anaesthetic with her COPD.

Post void bladder scan	35ml

What is the next best step in the patient's management?

Bladder wall injection with botulinum toxin	3%
[✓ Duloxetine]	72%
Intermittent self catheterisation	5%
No further management required	1%
Oxybutynin	19%

Duloxetine may be used in patients with stress incontinence who don't respond to pelvic floor muscle exercises and decline surgical intervention

Important for me Less important

Duloxetine is the correct answer. The incontinence described here is stress incontinence, which occurs due to a weakness in the pelvic floor. This leads to the release of a small amount of urine during episodes of raised intra-abdominal pressure. The symptoms of incontinence can also be seen where patients need to rush to get to the toilet when their bladder is full. The first-line treatment for stress incontinence pelvic floor exercises, which should be offered for a minimum of three months. Where this fails women should then be offered surgical intervention, in the form of colposuspension or autologous fascia slings. In the event that women do not respond to pelvic floor training and are not suitable for surgical intervention, then duloxetine can be offered.

The type of incontinence described is stress incontinence. Urge incontinence is where patients get the sudden urge to pass urine and then need to go to the toilet urgently to avoid episodes of incontinence. It is related to detrusor muscle overactivity.

Oxybutynin is a first-line management option for patients with urge incontinence. NICE recommends an acetylcholinergic medication with the lowest acquisition cost as the first-line therapy. Oxybutynin is the wrong answer for this presentation.

Intravesicular injection with botulinum toxin is recommended following and MDT review for patients with urge incontinence to reduce bladder overactivity but suppressing nerve impulses.

Intermittent self-catheterisation would be used in cases of overflow incontinence to use complete bladder emptying. The symptoms presented are similar to overflow incontinence, but the post-void bladder scan of 35ml rules this out.

No further management is incorrect as the patient finds the symptoms distressing and whilst the symptoms do not seem severe, the patient's needs should be addressed.

👍 👎 Discuss (6) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity

  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation
- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:
- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:
- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

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← Question 189 of 414 ✗ ⚐ →

What is the most common cause of primary hyperaldosteronism?

	Pituitary tumour	6%
	Adrenocortical adenoma	20%
	Adrenal carcinoma	2%
🟥	Ectopic secretion	2%
🟩	Bilateral idiopathic adrenal hyperplasia	71%

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Important for me Less important

👍 👎 Discuss (2) Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes

- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism

- adrenal carcinoma

Features

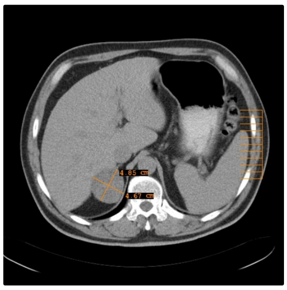
- **hypertension**
    - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
    - e.g. muscle weakness
    - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
    - hypertension with hypokalemia
    - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
    - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
    - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



Next question

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Question 190 of 414 ✗

Which one of the following is not part of the diagnostic criteria for the metabolic syndrome?

High triglycerides	11%
Low HDL	36%
🟩 High LDL	31%
Central obesity	7%
🟥 Hypertension	15%

High LDL levels are not part of the World Health Organization or International Diabetes Federation diagnostic criteria

Discuss (2) Improve

Next question

Metabolic syndrome

Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time. It is thought that the key pathophysiological factor is insulin resistance.

SIGN recommend using criteria similar to those from the American Heart Association. The similarity of the International Diabetes Federation criteria should be noted. For a diagnosis of metabolic syndrome at least 3 of the following should be identified:

- elevated waist circumference: men > 102 cm, women > 88 cm
- elevated triglycerides: > 1.7 mmol/L
- reduced HDL: < 1.03 mmol/L in males and < 1.29 mmol/L in females
- raised blood pressure: > 130/85 mmHg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

The International Diabetes Federation produced a consensus set of diagnostic criteria in 2005, which are now widely in use. These require the presence of central obesity (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors:

- raised triglycerides level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- reduced HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
- raised blood pressure: > 130/85 mm Hg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

In 1999 the World Health Organization produced diagnostic criteria which required the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

- blood pressure: > 140/90 mmHg
- dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
- central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
- microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

Other associated features include:

- raised uric acid levels
- non-alcoholic fatty liver disease
- polycystic ovarian syndrome

Next question

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Question 191 of 414 ✗

A 19-year-old woman is referred to endocrinology with irregular menses, excessive acne vulgaris and hirsutism. She reports she began to develop breasts and pubic hair at 8 years of age.

On examination there is clitoromegaly. Her BMI is 26 kg/m^2. She has mild male-pattern baldness.

Which of the following is the most likely deficiency?

	3-beta hydroxysteroid dehydrogenase deficiency	4%
	11-beta hydroxylase deficiency	23%
	17-alpha hydroxylase deficiency	17%
🟥	20,22-desmolase deficiency	1%
🟩	21-hydroxylase deficiency	54%

Congenital adrenal hyperplasia is most commonly due to 21-hydroxylase deficiency

Important for me Less important

The correct answer is 21-hydroxylase deficiency. The diagnosis is most likely to be congenital adrenal hyperplasia (CAH), given her history of irregular menses, acne, hirsutism, early breast and pubic hair development, clitoromegaly and male-pattern baldness. 21-hydroxylase deficiency is by far the most common cause, accounting for approximately 90% of cases.

3-beta hydroxysteroid dehydrogenase deficiency is a much rarer cause of CAH. A deficiency in this enzyme essentially leads to the same end result as a 21-hydroxylase deficiency, with largely the same signs and symptoms.

11-beta hydroxylase deficiency and 17-alpha hydroxylase deficiency are other rare causes of CAH.

20,22-desmolase deficiency is now known as lipoid congenital adrenal hyperplasia and is another rare subtype of CAH. It was originally thought to be due to a mutation in 20,22-desmolase, but this was later identified as cytochrome P450scc.

👍 👎 Discuss (4) Improve

Next question

Congenital adrenal hyperplasia ★

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders that impair adrenal steroid biosynthesis. The deficiency in cortisol production leads to compensatory overproduction of adrenocorticotropic hormone (ACTH) by the anterior pituitary. Elevated ACTH levels increase the production of adrenal androgens, which can result in the virilization of female infants and affect genital development.

Cause
- 21-hydroxylase deficiency (90%)
  - impairs the conversion of 17-hydroxyprogesterone to 11-deoxycortisol, leading to cortisol deficiency and excess androgen production
- 11-beta hydroxylase deficiency (5%)
  - results in hypertension due to excess deoxycorticosterone
- 17-hydroxylase deficiency (very rare)
  - leads to mineralocorticoid excess with low androgen and estrogen levels

Clinical features
- the symptoms and signs of CAH vary depending on the specific enzyme deficiency and the severity of the disorder. Common clinical presentations include:
- virilization:
  - female infants may present with ambiguous genitalia due to excessive androgen exposure in utero.
  - male infants appear normal at birth, which can delay diagnosis.
- salt-wasting crisis:
  - this severe form occurs in about 75% of cases with 21-hydroxylase deficiency
  - it is characterized by dehydration, hypotension, and electrolyte imbalances, and can be life-threatening if not treated promptly.
- precocious puberty: Excess androgens can lead to early development of secondary sexual characteristics in both males and females.
- infertility: Adults with untreated CAH may experience fertility issues due to hormonal imbalances.
- height and growth abnormalities: Children with CAH often experience accelerated growth rates initially but may have a shorter adult stature due to early epiphyseal closure.

Diagnosis

- many countries screen newborns for CAH, looking for elevated levels of serum concentration of 17-hydroxyprogesterone (17OHP). This is however not yet done in the UK
- ACTH stimulation testing is used to confirm the diagnosis
  - evaluates the adrenal gland's response to ACTH, with abnormal increases in 17OHP indicating CAH

Management

- primarily involves glucocorticoid replacement to reduce ACTH levels and minimize adrenal androgen production
- in cases of mineralocorticoid deficiency fludrocortisone is also prescribed

Image sourced from Wikipedia

Next question

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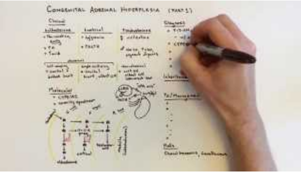
Media



Congenital Adrenal Hyperplasia (CAH) - 1 of 2

Quick Medical Genetics - YouTube 21 1

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Question 192 of 414 ✗

A 32 year-old man presents complaining of persistent headaches. He was diagnosed with hypertension 4 months ago and started on perindopril. On examination, heart his rate is 75 beats per minute and blood pressure is 185/115mmHg.

Investigations:

Serum potassium	1.9 mmol/L (3.5-5.0)
Plasma aldosterone (after 30 minutes supine)	700 pmol/L (135-400)
Plasma renin activity (after 30 minutes supine)	0.4 pmol/mL/hr (1.1-2.7)

What is the most likely cause of his hypertension?

	Addison disease	4%
	Bilateral renal artery stenosis	8%
🟥	Coarctation of the aorta	1%
	Phaeochromocytoma	6%
🟩	Primary hyperaldosteronism	82%

Primary hyperaldosteronism can present with hypertension, hypernatraemia, and hypokalemia

Important for me Less important

Primary hyperaldosteronism is typically caused by an aldosterone producing adenoma (Conn's syndrome), other causes include: bilateral adrenocortical hyperplasia and adrenal carcinoma.

Primary hyperaldosteronism and bilateral renal artery stenosis are associated with hypokalaemia due raised serum aldosterone, which causes increased sodium reabsorption and potassium excretion.

Aldosterone is elevated in bilateral renal artery stenosis due to reduced renal perfusion. Aldosterone is high in primary hyperaldosteronism, however, serum renin is usually low in primary hyperaldosteronism due to the resulting hypertension causing excessive renal perfusion, which results in decreased renin production (negative feedback mechanism). High renin levels are seen in renal artery stenosis as renal perfusion is permanently reduced, despite hypertension, due to the stenotic renal arteries.

(Reference: Oxford handbook of clinical medicine, 8th ed.pg.220)

👍 👎 Discuss (6) Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes

- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

Features

- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

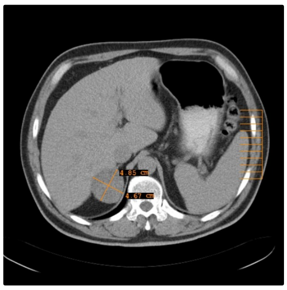
Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension

- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
  - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



Next question

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Links

The Endocrine Society 👍 5 👎 3

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Question 193 of 414 ✗

A 33-year-old woman is referred to the gynaecology outpatient department with a three-month history of post-coital and intermenstrual bleeding. She has a past medical history of ankylosing spondylitis. She is on regular certolizumab. She smokes ten cigarettes per day and drinks three bottles of wine per week. She has been in a regular sexual relationship with one male partner for the last eleven months and has been on the combined oral contraceptive for that time period. She has never been pregnant.

A gynaecological examination is unremarkable.

Colposcopy is undertaken, which demonstrates a stage I squamous cell carcinoma.

Given the likely diagnosis, what is her most significant risk factor for the development of this condition from the options listed below?

	Alcohol use	1%
	Certolizumab treatment	5%
	Combined oral contraceptive pill use	8%
🟥	Parity	4%
🟩	Smoking	82%

Women who smoke are at a two-fold increased risk of developing cervical cancer than women who do not

Important for me Less important

Human papillomavirus (HPV) infection is by far the most important cause of cervical cancer. However, from the options listed, smoking is the most definitive risk factor that this woman has for the development of cervical cancer. Colposcopy is the method used to diagnose cervical cancer. Stage I means that the cancer is confined to the cervix. Smoking doubles the risk of developing cervical cancer compared to women who do not smoke.

Alcohol use is incorrect. While she drinks more than the recommended guidelines suggest, this is not associated with the development of cervical cancer.

Certolizumab treatment is incorrect. Although there have been some large studies that suggest a link between anti-TNF treatment and the development of cervical cancer in patients with severe rheumatoid arthritis, it was difficult to disentangle whether or not this neoplasm was related to the severity of rheumatoid arthritis or the treatment itself. There have been no studies proving a link between anti-TNF treatment in patients with ankylosing spondylitis and the development of cervical cancer.

Combined oral contraceptive pill use is incorrect. The long term use of oral contraceptive medication may be associated with an increased risk of cervical cancer but this patient has only been taking this medication for a short period of time (11 months).

Parity is incorrect. High parity rather than low parity is associated with the development of cervical cancer.

👍 👎 Discuss (1) Improve

Next question

Cervical cancer

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. It may be divided into:

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papillomavirus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status

- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer
- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov 10;370(9599):1609-21) confirmed the link

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Cancer Research UK 👍 0 👎 0

Cervical cancer

Clinical Knowledge Summaries 👍 0 👎 3

Cervical cancer management guidelines

Report broken link

Media

PassMedicine

Question 194 of 414 ✗

A 33-year-old woman presents with weight loss and excessive sweating. her partner reports that she is 'on edge' all the time and during the consultation you notice a fine tremor. Her pulse rate is 96/min. A large, non-tender goitre is noted. Examination of her eyes is unremarkable with no evidence of exophthalmos.

Free T4	26 pmol/l
Free T3	12.2 pmol/l (3.0-7.5)
TSH	< 0.05 mu/l

What is the most likely diagnosis?

	Toxic multinodular goitre	23%
	Hashimoto's thyroiditis	7%
	T3-secreting adenoma	5%
🟥	De Quervain's thyroiditis	5%
🟩	Graves' disease	60%

Graves' disease is the most common cause of thyrotoxicosis

Important for me Less important

Only around 30% of patients with Graves' disease have eye disease so the absence of eye signs does not exclude the diagnosis.

Discuss (7) Improve

Next question

Graves' disease: features

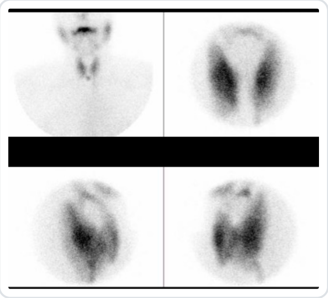
Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis
- eye signs (30% of patients)
    - exophthalmos
    - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
    - digital clubbing
    - soft tissue swelling of the hands and feet
    - periosteal new bone formation

Autoantibodies
- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

Thyroid scintigraphy
- diffuse, homogenous, increased uptake of radioactive iodine



Next question

PassMedicine

Question 195 of 414 ✓

A 45-year-old man attends a clinic for a diabetic review. He is currently on the maximal dose of metformin.

Blood results are as follows:

Hb	152 g/L	Male: (135-180) Female: (115 - 160)
Platelets	162 * 10^9/L	(150 - 400)
WBC	8.4 * 10^9/L	(4.0 - 11.0)
Na^+	138 mmol/L	(135 - 145)
K^+	3.6 mmol/L	(3.5 - 5.0)
Urea	7.4 mmol/L	(2.0 - 7.0)
Creatinine	96 µmol/L	(55 - 120)
CRP	2 mg/L	(< 5)

HbA1c	68mmol/mol	(<48)

He is started on repaglinide and is counselled about the side effects which include hypoglycaemia.

What is the mechanism of action of this drug?

Activates peroxisome proliferator-activated receptors (PPARs) leading to increased insulin sensitivity	16%
Activates the incretin receptor	11%
Binds to an ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells	59%
Inhibits the action of DPP4	9%
Inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK	5%

Meglitinides - bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells

Important for me Less important

Binds to an ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells is correct. Meglitinides (e.g. repaglinide, nateglinide) bind to an ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells thereby resulting in increased insulin secretion. The most frequent adverse effect of meglitinides is hypoglycemia.

Inhibits the action of DPP4 is incorrect. DPP4 inhibitors include sitagliptin and alogliptin. DPP4 is an enzyme that deactivates the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. The inhibition of this enzyme causes an increased availability of GLP-1 levels in the body.

Activates the incretin receptor is incorrect. Glucagon-like peptide (GLP-1), an incretin, is a gastrointestinal peptide involved in the regulation of glucose levels where the hormone is released upon consuming food. It stimulates insulin formation and release. GLP1 agonists stimulate the GLP1 or incretin receptor. Drugs in this class include exenatide and liraglutide.

Inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK is incorrect. This is the mechanism of action of metformin which inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK, enhancing insulin sensitivity (via effects on fat metabolism) and lowering cAMP, thus reducing the expression of gluconeogenic enzymes. Metformin does not cause hypoglycaemia.

Activates peroxisome proliferator-activated receptors (PPARs) leading to increased insulin sensitivity is incorrect. Thiazolidinediones, such as pioglitazone, are synthetic ligands for peroxisome proliferator-activated receptors (PPARs). Activation of these receptors leads to increased sensitivity to insulin. These agents do not cause hypoglycaemia.

👍 👎 Discuss (2) Improve

Next question

Meglitinides ★

Meglitinides (e.g. repaglinide, nateglinide)

- increase pancreatic insulin secretion
- like sulfonylureas they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells
- often used for patients with an erratic lifestyle

- adverse effects include weight gain and hypoglycaemia (less so than sulfonylureas)

Next question

Textbooks

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Score: **24.1%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗
16	✗

PassMedicine

Question 196 of 414 ✗

A 23-year-old woman is seen at the maternity clinic after urine and blood testing confirm she is pregnant. Based on her last menstrual dates she is estimated to be approximately 9 weeks pregnant.

The patient has established hypothyroidism following a thyroidectomy several years previous but is well controlled on thyroxine. This is her second pregnancy with her first being two years ago in which she delivered at 39 weeks with no complications.

What change to their established medication may be required for patients such as this?

Changed to a different agent	1%
Increase by up to 100%	2%
🟥 Increase by up to 20%	11%
🟩 Increase by up to 50%	69%
No change required at this stage of the pregnancy	16%

Women with hypothyroidism may need to increase their thyroid hormone replacement dose by up to 50% as early as 4-6 weeks of pregnancy

Important for me Less important

During pregnancy the medications patients are previously established on may have to undergo dose adjustments due to increased metabolism or increased requirement. In pregnancy, there is an increase in thyroid-binding globulin (TBG), an increase in urinary iodine excretion and deiodinase activity of the placenta which increase thyroid hormone metabolism. As a result, there is an increased thyroid hormone demand and a patient's thyroxine dose may have to be **increased by up to 50%** as early as 4-6 weeks into a pregnancy. Thyroid-stimulating hormone testing can be used to guide this dosing adjustment and should be conducted in each trimester and 6-8weeks post-partum as a minimum.

Some medications may have to be stopped during pregnancy and **changed to a different agent**, particularly within the first trimester, due to an increased risk of congenital abnormalities associated with certain drugs. Thyroxine however is safe to use throughout pregnancy, as well as during breastfeeding, with no associated risk established.

Due to multiple factors, there is both an increased demand as well as an increased metabolism of thyroxine in pregnancy therefore most patients require a higher dose increase than only **20%**.

Although a dose increase of thyroxine is required in a large proportion of patients when they become pregnant an increase of over 50% is extremely rare. An **increase by up to 100%** should not be required in a hypothyroid patient if their condition was stable prior to becoming pregnant and if clinical features or thyroid function testing are still abnormal despite an increase up to 50% then other causes should be investigated for.

It is extremely rare for hypothyroid patients to require **no change** in their thyroxine dose when they become pregnant. An increase in dosing may be required as early as 4-6 weeks into a pregnancy.

👍 | 👎 | 💬 Discuss | Improve

Next question

Pregnancy: thyroid problems ★

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'

- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

PassMedicine

Question 197 of 414 ✗

A 62-year-old woman has attended the diabetes clinic for review.

She was diagnosed with type 2 diabetes five years ago and has, until recently, been well managed with metformin 1g twice daily and gliclazide 160mg once daily.

The latest HbA1c is below.

HbA1c	62 mmol/mol	(20-41)

The consultant has advised commencing a medication to increase levels of incretins in an attempt to optimise the patient's HbA1c.

What is the most appropriate medication to commence?

	Dapagliflozin	7%
	Glimepiride	3%
	Liraglutide	25%
🟥	Pioglitazone	5%
🟩	Sitagliptin	61%

DPP-4 inhibitors increase levels of incretins such as GLP-1 and GIP

Important for me Less important

Dipeptidyl peptidase-4 (DPP-4) inhibitors decrease the peripheral breakdown of incretins, thus increasing plasma concentration. **Sitagliptin** is the only option from above that is a DPP-4 inhibitor, making this the correct answer.

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. They work by reducing glucose reabsorption in the kidney leading to lower circulating glucose. SGLT2 inhibitors cause glucosuria and are associated with an increased risk of urinary tract infections and candidal infections.

Glimepiride is a sulphonylurea and acts by stimulating insulin secretion. This would also not be co-prescribed with another sulphonylurea, in this case, gliclazide.

Liraglutide is a glucagon-like peptide-1 (GLP-1) mimetic. It acts in the same way as incretins by increasing insulin secretions. Unlike DPP-4 inhibitors, GLP-1 mimetics do not increase incretin levels.

Pioglitazone is a thiazolidinedione that acts by increasing insulin sensitivity in peripheral tissues. It does not act via incretins. Pioglitazone is rarely prescribed due to the side effect and risk profile, especially its increased risk of bladder cancer.

Discuss (3) Improve

Next question

Diabetes mellitus: GLP-1 drugs

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

High-yield textbook

Extended textbook

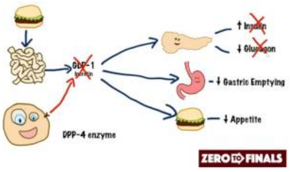
Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

Report broken link

Media



↑ Insulin
↓ Glucagon
GLP-1
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2

The role of "GLP" system in tt of diabetes
Sitagliptin
(-)
inactive GLP-1
DPP-4
incretin
"GLP-1"
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

PassMedicine

Question 198 of 414 ✓

A 27-year-old man presents to the emergency department with severe abdominal pain and vomiting. He is visibly distressed. His heart rate is 97bpm, his blood pressure is 106/66 mmHg and his respiratory rate is 25/min with oxygen saturation of 96% on room air.

His venous blood gas shows the following:

pH	7.13	7.35 - 7.45
pO2	6.2 kPa	4.0 - 5.3
pCO2	3.6 kPa	5.5 - 6.8
HCO3	12.3 mmol/L	22.0 - 28.0
Base excess	3.6 mEq/L	-2 - +2
Na	148 mmol/L	135 - 145
K	5.0 mmol/L	3.5 - 5.0
Glucose	25.7 mmol/L	4.0 - 11.0
Lactate	6 mmol/L	0.5 - 1.6

Blood ketones are 3.7 mmol/L.

What first-line treatment should be commenced?

1L of IV 0.45% sodium chloride over 1 hour	4%
1L of IV 0.9% sodium chloride over 1 hour	72%
500ml of IV 0.45% sodium chloride over 5 minutes	2%
500ml of IV 0.9% sodium chloride over 5 minutes	10%
IV insulin infusion at 0.1 unit/kg/hour	12%

Diabetic ketoacidosis: isotonic saline should be used initially, even if the patient is severely acidotic

Important for me Less important

This patient has diabetic ketoacidosis, confirmed by his blood gas and blood ketones. He is severely acidotic but his systolic blood pressure is not less than 90 mmHg. In DKA patients will typically be in a fluid deficit of around 7 litres. Treatment typically should replace 50% of fluid within the first 12 hours of treatment when patients are not at risk of developing fluid overload. Hence initial management should be **1L 0.9% sodium chloride administered over 1 hour**.

If his blood pressure were to be less than 90mmHg a **500ml of 0.9% sodium chloride over 5 minutes** would be appropriate for initial management. Given that his blood pressure is above 90mmHg systolic, this is the incorrect answer.

1L of 0.45% sodium chloride over 1 hour should only be administered in an intensive care setting and would not be appropriate initial management. 0.9% sodium chloride should always be tried initially.

500ml of IV 0.45% sodium chloride over 5 minutes would not be appropriate, both because 0.45% sodium chloride is only administered in intensive care settings, but also this form of fluid would not usually be given in the form of boluses as it risks rapid shifts in sodium concentration.

Insulin infusion would be appropriate for this patient, however, as per the joint British diabetes societies DKA guidelines, sodium chloride should always be the first-line management, even before insulin.

Discuss (5) Improve

Next question

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) may be a complication of existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

Pathophysiology

- DKA is caused by uncontrolled lipolysis (not proteolysis) which results in an excess of free fatty acids that are ultimately converted to ketone bodies

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction.

Features
- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l • anion gap > 10 • ketonaemia	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l • ketones > 3 mmol/l or urine ketones ++ on dipstick

Management

Main principles of management
- fluid replacement
  - most patients with DKA are deplete around 5-8 litres
  - isotonic saline is used initially, even if the patient is severely acidotic
  - please see an example fluid regime below.
- insulin
  - an intravenous infusion should be started at 0.1 unit/kg/hour
  - once blood glucose is < 14 mmol/l an infusion of 10% dextrose should be started at 125 mls/hr *in addition* to the 0.9% sodium chloride regime
- correction of electrolyte disturbance
  - serum potassium is often high on admission despite total body potassium being low
  - this often falls quickly following treatment with insulin resulting in hypokalaemia
  - potassium may therefore need to be added to the replacement fluids
  - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- long-acting insulin should be continued, short-acting insulin should be stopped

JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

Fluid	**Volume**
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	**Potassium replacement in mmol/L of infusion solution**
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Resolution

DKA resolution is defined as:
- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

Further points
- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist

- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

Complications

Complications may occur from DKA itself or the treatment:

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Joint British Inpatient Diabetes Societies Inpatient Care Group 👍 8 👎 4

PassMedicine

Question 199 of 414 ✗

A 56-year-old man presents to his GP with a 6-year history of hypertension that has been difficult to control. Several medications have been tried but none have been successful in controlling his blood pressure. He also describes a generalised muscle weakness and nocturia for many years. He has no significant past medical history.

On examination, he appears well. His blood pressure is measured as 162/86 mmHg. Blood tests are taken and the results are as follows:

Na^+	138 mmol/L	(135 - 145)
K^+	3.2 mmol/L	(3.5 - 5.0)
Urea	5.6 mmol/L	(2.0 - 7.0)
Creatinine	78 µmol/L	(55 - 120)
Aldosterone:renin ratio	42 ng/dl per ng/(ml·h)	(2-17)

Given the above, which of the following is the most likely cause?

	Adrenal adenoma	18%
	Adrenocortical carcinoma	2%
🟩	Bilateral idiopathic adrenal hyperplasia	71%
	Ectopic aldosterone-producing adenoma	7%
🟥	Unilateral adrenal hyperplasia	3%

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Important for me Less important

The history and low potassium here point strongly towards primary hyperaldosteronism, which is the most common treatable/curable cause of hypertension. The most common cause of this is bilateral idiopathic adrenal hyperplasia - approximately 66% of cases. Although the classic textbook presentation includes hypokalaemia, in reality, most patients are normokalaemic.

An adrenal adenoma is incorrect - this was previously thought to be the most common cause of primary hyperaldosteronism - also known as Conn's syndrome. Recent studies, however, have demonstrated that bilateral idiopathic adrenal hyperplasia is more common, with adrenal adenomas accounting for just 33% of cases.

Adrenocortical carcinoma is an incredibly rare cause of primary hyperaldosteronism - accounting for <1% of all cases of primary hyperaldosteronism.

Ectopic aldosterone-producing adenomas are also incredibly rare - <0.1% of all cases.

Unilateral adrenal hyperplasia is also far less common than bilateral idiopathic adrenal hyperplasia - not as rare as the previous two, but still only accounting for approximately 2% of all cases.

👍 👎 💬 Discuss (1) Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes
- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

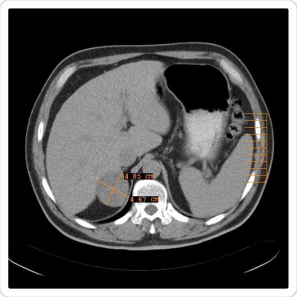
Features
- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
    - hypertension with hypokalemia
    - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
    - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
    - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



Next question

Textbooks

High-yield textbook

Extended textbook

PassMedicine

Question 200 of 414 ✗

A 47-year-old woman is referred to the general medical clinic. She has gained 10 kg in weight in the past 3 months but her main problem is episodic sweating. These episodes of sweating are associated with double vision and typically occur early in the morning. Clinical examination is unremarkable. What is the most likely diagnosis?

Bronchial carcinoid	8%
Hashimoto's thyroiditis	9%
Menopause	8%
🟥 Cushing's syndrome	20%
🟩 Insulinoma	56%

This is a typical presentation of insulinoma

Discuss (5) Improve

Next question

Insulinoma

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics
- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

Features
- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen

- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis

- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Management

- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

Next question

Textbooks

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Media

Pancreatic
Neuroendocrine
Neoplasms

Pancreatic neuroendocrine neoplasms

Osmosis - YouTube 👍 19 👎 0

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← Question 201 of 414 ✗ →

A 29-year-old woman attends a routine clinical review. She is 25 weeks into her first pregnancy. She describes that she has been feeling more tired over the past four months, during which time she has gained 3kg in weight. She has no significant past medical history. Her mother suffers from Crohn's disease.

Her thyroid function tests are shown below:

TSH	0.7mIU/L	(0.5 - 5.0)
Total T3	3.1nmol/L	(0.9 - 2.5)
fT3	4.3pmol/L	(3.1 - 6.8)
Total T4	195nmol/L	(50 - 160)
fT4	16.0pmol/L	(12 - 22)

What is the most likely explanation for these results?

Hyperthyroidism	4%
Hypothyroidism	2%
Normal pregnancy	70%
Subclinical hyperthyroidism	16%
Subclinical hypothyroidism	8%

Raised total T3 and T4 but normal fT3 and fT4 suggest high concentrations of thyroid binding globulin, which can be seen during pregnancy

Important for me Less important

The correct answer is **normal pregnancy**. This patient has a normal TSH, with normal fT3 and fT4 levels, suggesting normal thyroid function. The elevated levels of total T3 and T4 can be explained by the high concentrations of thyroid-binding globulin that are often seen during pregnancy. Although the patient has reported some fatigue and minor weight gain, these symptoms are non-specific in the context of pregnancy and do not necessarily point towards thyroid dysfunction.

Hyperthyroidism is incorrect. This would be associated with an abnormally suppressed TSH and raised levels of fT3 and fT4.

Hypothyroidism is incorrect. Although the patient's symptoms are seen in many patients with hypothyroidism, this would tend to be associated with a raised TSH and decreased fT3 and fT4.

Subclinical hyperthyroidism is incorrect. This would tend to be characterised by an isolated suppressed TSH, with normal fT3 and fT4 and an absence of symptoms of thyroid dysfunction.

Subclinical hypothyroidism is incorrect. This would normally present with an isolated elevated TSH, with normal fT3 and fT4.

👍 👎 Discuss (2) Improve

Next question

Pregnancy: thyroid problems

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism

- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

PassMedicine

Question 202 of 414 ✓

A 45-year-old man is investigated following referral to the endocrinology clinic with polydipsia. Plasma glucose and calcium are normal. A water deprivation test is performed with the following results:

Starting plasma osm.	319 mOsmol/l (275-295 mOsmol/l)
Final urine osm.	142 mOsmol/l
Urine osm. post-DDAVP	885 mOsmol/l

What is the most likely diagnosis?

Psychogenic polydipsia	11%
Nephrogenic diabetes insipidus	14%
Primary hyperparathyroidism	1%
Pseudohypoparathyroidism	1%
Cranial diabetes insipidus	73%

A dramatic improvement is seen in the ability of the kidneys to concentrate urine following the administration of DDAVP. This points towards a diagnosis of cranial diabetes insipidus

Discuss (6) Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method

- prevent patient drinking water

- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

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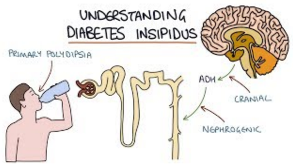
UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5

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Question 203 of 414 ✗

A 55-year-old lady with known metastatic breast cancer presents to the acute medical take with hypercalcaemia. She has no other co-morbidities, is a non-smoker and works in an office based job. She is treated with intravenous fluid and bisphosphonates, after which her calcium normalises and she is discharged.

At discharge, she is referred to the endocrinology department for outpatient follow-up, alongside regular blood calcium monitoring. What verbal advice is it most important to give her on discharge from hospital?

	Avoid excess exercise until treated	5%
	Low calcium diet	11%
🟥	Reduce alcohol intake	6%
	Ensure adequate sunlight exposure	6%
🟩	Increase fluid intake	72%

In the context of hypercalcaemia secondary to malignancy the below advice is suggested by NICE:

- Advice about maintaining good hydration (drinking 3-4 L of fluid per day), provided there are no contraindications (such as severe renal impairment or heart failure).
- Reassure that a low calcium diet is not necessary, as intestinal absorption of calcium is usually reduced.
- Advise the person to avoid any drugs or vitamin supplements that could exacerbate the hypercalcaemia.
- Encourage mobilization where possible to avoid exacerbating the hypercalcaemia.
- Advise the person to report any symptoms of hypercalcaemia.

NICE Guidelines: Hypercalcaemia - http://cks.nice.org.uk/hypercalcaemia)

Discuss (3) | Improve

Next question

Hypercalcaemia: management ★

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

Loop diuretics such as furosemide are sometimes used in hypercalcaemia, particularly in patients who cannot tolerate aggressive fluid rehydration. However, they should be used with caution as they may worsen electrolyte derangement and volume depletion.

Next question

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Royal College of Physicians 👍 2 👎 3

Hypercalcaemia â€“ presentation and management

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Media

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← Question 204 of 414 ✕ ⚐ →

A 51-year-old woman who is known to have poorly controlled type 1 diabetes mellitus is reviewed. Her main presenting complaint is bloating and vomiting after eating. She also notes that her blood glucose readings have become more erratic recently. Which one of the following medications is most likely to be beneficial?

	Helicobacter pylori eradication therapy	9%
	Lansoprazole	11%
🟥	Amitriptyline	7%
🟩	Metoclopramide	68%
	Cyclizine	4%

The true prevalence of gastroparesis in patients with type 1 diabetes mellitus is not known but most modern studies estimate around 5% are affected. This leads to both upper gastrointestinal symptoms and erratic glucose control due to gastric emptying dysfunction. Metoclopramide is a pro-kinetic drug that can improve gastric emptying.

Discuss (1) Improve

Next question

Diabetic neuropathy

Peripheral neuropathy

Diabetes typically leads to sensory loss and not motor loss. Sensory loss typically results in a 'glove and stocking' distribution, with the lower legs affected first due to the length of the sensory neurons supplying this area. Painful diabetic neuropathy is also a common problem in clinical practice.

NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

Gastrointestinal autonomic neuropathy

Gastroparesis

- occurs secondary to autonomic neuropathy
- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

Chronic diarrhoea

- often occurs at night

Gastro-oesophageal reflux disease

- caused by decreased lower esophageal sphincter (LES) pressure

Next question

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Question 205 of 414 ✗

A 38-year-old male presents to the emergency department with nausea and confusion. He has a background medical history of bipolar affective disorder, type two diabetes mellitus, alcohol dependency and he was recently in a road traffic accident where he sustained a minor head injury. His regular medications include lithium, carbamazepine, and metformin. He has been binge drinking more than 28 units of alcohol at a time for the last 3 months. On examination, he appears euvolemic.

Further investigations reveal:

Na^+	119 mmol/L	(135 - 145)
Serum osmolality	264 mOsm/kg	(275 - 300)
Urinary sodium	42 mEq/L	
Urine osmolality	556 mOsm/kg	(50 - 1200)
Lithium level	1.4 mmol/L	(0.4 - 1.0)

What is the most likely cause for this patient's hyponatremia?

🟥	Alcohol binge drinking	21%
🟩	Carbamazepine	28%
	Cranial diabetes insipidus secondary to head trauma	14%
	Lithium	36%
	Metformin	1%

SIADH - drug causes: carbamazepine, sulfonylureas, SSRIs, tricyclics

Important for me Less important

Carbamazepine is the correct answer. The above clinical scenario is consistent with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Carbamazepine tricyclic antidepressants, serotonin selective reuptake inhibitors (SSRIs), and sulfonylureas are known to cause SIADH. SIADH causes hyponatremia with low serum osmolality and concentrated urine (urinary sodium

>40 mEq/L) with inappropriate urine osmolality (>100 mOsm/kg) levels. In the setting of serum hypotonicity (serum osmolality <275 mOsm/kg), it is expected that the urine osmolality would be <100 mOsm/kg. These are the key features of SIADH.

Alcohol binge drinking is an incorrect answer. Alcohol bingeing can lead to ADH suppression in the posterior pituitary gland subsequently leading to polyuria. This is similar to cranial diabetes insipidus or partial cranial diabetes insipidus and typically causes hypernatremia with a raised serum osmolality and decreased urine osmolality. This is clearly inconsistent with the hyponatremia with low serum osmolality in this scenario.

Cranial diabetes insipidus secondary to head trauma is an incorrect answer. Diabetes insipidus is characterised by hypernatremia with a raised serum osmolality and decreased urine osmolality. This is inconsistent with the scenario above. The road traffic accident and minor head trauma in the patient's history is a red herring.

Lithium is an incorrect answer. Lithium is associated with diabetes insipidus rather than SIADH. Diabetes insipidus is characterised by hypernatremia with a raised serum osmolality and decreased urine osmolality. Although lithium toxicity can cause nausea and confusion, it is important to note that the question is asking for the most likely cause of this patient's hyponatremia and not his presenting symptoms. Additionally, this patient has a supratherapeutic lithium level (1.4 mmol/L), however, lithium toxicity is not typically seen with levels <1.5 mmol/L. Mild symptoms, including nausea, fatigue, and tremor occur at lithium levels between 1.5 to 2.5 mmol/L. Moderate symptoms, including confusion, tachycardia, ataxia, and hypertonia occur at lithium levels between 2.5 to 3.5 mmol/L. Severe symptoms, including hyperthermia, hypotension, seizures and coma occur at lithium levels between >3.5 mmol/L.

Metformin is an incorrect answer. Metformin is not associated with SIADH. However, sulfonylureas, such as glimepiride and glipizide, are associated with SIADH.

👍 👎 Discuss (8) Improve

Next question

Syndrome of inappropriate ADH secretion ★

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention. Patients with SIADH are typically euvolemic, i.e. they do not show signs of overt volume depletion or overload.

Pathophysiology

- SIADH involves an excessive release of antidiuretic hormone (ADH), also known as vasopressin, which leads to water retention, volume expansion, and dilutional hyponatraemia
- ADH is produced by the hypothalamus and stored in the posterior pituitary gland. Its primary function is to regulate the body's water balance
- It does this by increasing water reabsorption in the collecting ducts of the kidneys, thereby decreasing the volume of urine produced
- In SIADH, there is an inappropriate and continuous release of ADH that is not inhibited by normal physiological mechanisms, such as adequate or excess body fluid levels
- As a result, the kidneys reabsorb more water, leading to decreased urine output, and expansion of extracellular fluid volume.
- Importantly, this increase in body fluid volume does not lead to the expected signs of fluid overload, such as oedema or hypertension, because the excess fluid is uniformly distributed throughout all body fluid compartments.
- However, as water is retained in the body, the concentration of electrolytes in the blood, particularly sodium, becomes diluted, leading to hyponatraemia.

Causes of SIADH

Category	**Examples**
Malignancy	• **small cell lung cancer** • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• sulfonylureas* • SSRIs, tricyclics • carbamazepine • vincristine • cyclophosphamide
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias

Investigations

- Urine osmolality: Urine osmolality is inappropriately high (>100 mOsm/kg) in relation to serum osmolality, as the kidneys should normally dilute urine in the setting of low serum osmolality.
- Urine sodium concentration: Urine sodium concentration is typically high (>40 mmol/L) due to the action of ADH on the renal tubules.

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

Next question

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WHAT IS...
SIADH?

Syndrome of inappropriate antidiuretic hormone (SIADH)

PassMedicine

← Question 206 of 414 ✕ →

A 22-year-old female presents with recurrent painful oral ulceration. Examination reveals signs of oral *Candidal* infection. Which one of the following would most suggest type 1 polyglandular syndrome?

🟩	Hypocalcaemia	29%
	Rheumatoid arthritis	6%
	Type II diabetes mellitus	17%
🟥	Coeliac disease	21%
	Hypercalcaemia	27%

Primary hypoparathyroidism is usually the first endocrine manifestation of type 1 autoimmune polyendocrinopathy syndrome. The contrast to multiple endocrine neoplasia (MEN), where hyperparathyroidism is a common finding, should be noted

The question gives a slightly atypical history as this is the upper end of the age range in which patients would be expected to present

Discuss (8) Improve

Next question

Autoimmune polyendocrinopathy syndrome

Addison's disease (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients. There are two distinct types of autoimmune polyendocrinopathy syndrome (APS), with type 2 (sometimes referred to as Schmidt's syndrome) being much more common.

APS type 2 has a polygenic inheritance and is linked to HLA DR3/DR4. Patients have Addison's disease plus either:

- type 1 diabetes mellitus

- autoimmune thyroid disease

APS type 1 is occasionally referred to as Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC). It is a very rare autosomal recessive disorder caused by mutation of AIRE1 gene on chromosome 21

Features of APS type 1 (2 out of 3 needed)

- chronic mucocutaneous candidiasis (typically first feature as young child)
- Addison's disease
- primary hypoparathyroidism

Vitiligo can occur in both types

Next question

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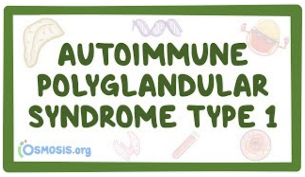

Autoimmune polyglandular syndrome type 1

Osmosis - YouTube 👍 18 👎 1

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← Question 207 of 414 ✗ ⚑ →

A 21-year-old student is brought into the Emergency Department by his friends, who are concerned about a recent change in his behaviour. They report that they had attended a nightclub with him the previous evening, during which time he had seemed only slightly intoxicated. They are not sure whether he has taken any illicit substances, but report that he was drinking unusually large quantities of water towards the end of the night.

On examination, the patient is obtunded, with a Glasgow Coma Scale score of 10 (E2 M5 V3). There are no focal neurological deficits on examination. He appears slightly hypervolaemic.

His blood test results are as follows:

Hb	120 g/L	Male: (135-180) Female: (115 - 160)
Platelets	170 * 10^9/L	(150 - 400)
WBC	4.8 * 10^9/L	(4.0 - 11.0)
Na^+	109 mmol/L	(135 - 145)
K^+	3.1 mmol/L	(3.5 - 5.0)
Bicarbonate	23 mmol/L	(22 - 29)
Urea	1.2 mmol/L	(2.0 - 7.0)
Creatinine	58 µmol/L	(55 - 120)

During the examination, the patient has a tonic-clonic seizure, which terminates after the administration of 4mg of intravenous lorazepam.

On his way to the Intensive Care Unit, he undergoes a CT scan of the brain, the results of which are as follows:

CT brain	Moderate, diffuse cerebral oedema with no evidence of haemorrhage, intracranial masses or fractures

What is the next most appropriate management step?

Start demeclocyline	7%
Initiate fluid restriction of 750ml per 24 hours	11%

Commence a 1000ml 0.9% NaCl infusion over eight hours	4%
Administer 30% NaCl	3%
Administer intravenous 3% NaCl	75%

Hypertonic saline is usually indicated in patients with acute, severe, symptomatic hyponatraemia (< 120 mmol/L)

Important for me Less important

This patient has presented with severe, acute hyponatraemia, as evidenced by the finding of cerebral oedema, and the onset of seizure activity. The question stem points towards the likely cause for this being ecstasy/MDMA use at a nightclub. MDMA can cause acute hyponatraemia due to a combination of syndrome of inappropriate antidiuretic hormone (SIADH) and psychogenic polydipsia. The blood test results suggest considerable haemodilution in keeping with polydipsia. This patient's hyponatraemia requires urgent, rapid correction with intravenous 3% (hypertonic) saline, as per the most recent NICE Clinical Knowledge Summary for the management of hyponatraemia in secondary care.

Demeclocycline is a medication used in the management of chronic hyponatraemia due to SIADH. It acts by inhibiting the G-protein coupled receptor signalling downstream of ADH binding to renal vasopressin V2 receptors, thus inducing nephrogenic diabetes insipidus. The half-life/ time taken till onset of demeclocyline means it would not be effective at rapidly increasing serum sodium concentrations in this patient.

Initiating a fluid restriction of 750ml per 24 hours would be a reasonable option in confirmed chronic or mild hyponatraemia due to SIADH, but would not be elevate this patient's dangerously low sodium levels rapidly enough.

0.9% NaCl is theoretically isotonic; administering 0.9% NaCl would not address this patient's severe hypotonicity due to excessive water intake, and would potentially exacerbate the portion of his hyponatraemia attributed to SIADH.

Whilst administering hypertonic saline is indicated in this scenario, 30% NaCl is a grossly hypertonic solution which would cause profound fluid shifts, and, unlike 3% NaCl, is not licensed or recommended by NICE.

👍 👎 💬 Discuss Improve

Next question

Hyponatraemia: treatment ★

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:

- duration of hyponatremia: is it acute or chronic?
  - acute: develops over a period of < 48 hours
  - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
  - mild: 130-134 mmol/L
  - moderate: 120-129 mmol/L
  - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
  - patients with mild hyponatraemia may be symptomatic
  - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
  - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
  - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
  - euvolemic hyponatraemia: SIADH
  - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected

- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
    - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
    - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider medications:
    - demeclocycline
    - vaptans (see below)

If a hypervolemic cause is suspected

- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):

- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia

- pathophysiology:
    - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
    - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
    - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
    - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
    - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

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Royal College of Physicians 15 3

2017 Hyponatraemia â€“ presentations and management

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Question 208 of 414 ✗

You are reviewing a 34-year-old woman in endocrine clinic. She had a total thyroidectomy 6 months ago for a toxic multinodular goitre.

Her thyroid-stimulating hormone (TSH) level today is 2.7 mU/L. She is currently taking 100 micrograms of levothyroxine daily.

She is keen on trying to conceive as soon as possible and has already started to take folic acid supplements. She has requested your advice on how to manage her levothyroxine.

What would be the most appropriate advice to give her?

	Continue current dose until first antenatal appointment at 8-10 weeks	12%
🟥	Reduce to 75 micrograms immediately and recheck TSH in 6 weeks	3%
🟩	Continue current dose but increase to 125 micrograms when 4-6 weeks pregnant	42%
	Increase to 150 micrograms immediately and recheck TSH in 6 weeks	29%
	Continue current dose but increase to 200 micrograms once pregnancy confirmed	14%

Women with hypothyroidism may need to increase their thyroid hormone replacement dose by up to 50% as early as 4-6 weeks of pregnancy

Important for me Less important

Suboptimally treated hypothyroidism in pregnancy is associated with reproductive complications, including miscarriage, anaemia, pre-eclampsia, placental abruption, postpartum haemorrhage and stillbirth. There are also adverse neonatal outcomes including preterm delivery, low birth weight, congenital abnormalities and impaired fetal neurocognitive development.

There is an increased demand for thyroxine during pregnancy, hence it is recommended to increase levothyroxine dose by 25-50% as early as 4-6 weeks gestation, which usually corresponds when a woman discovers she is pregnant. As neuro-development occurs early in the stages of fetal development, delaying action until the first antenatal appointment (which usually occurs at 8-10 weeks of pregnancy) would be inappropriate.

Her current thyroid-stimulating hormone (TSH) level is satisfactory, hence it is not necessary to adjust the dose immediately. A TSH of approximately 2.5 mU/L is thought to be optimal for conception and sustaining an early pregnancy. Had her results not been in the euthyroid range, it would be appropriate to advise delaying conception until treatment is stabilised.

Increasing the dose to 200 micrograms daily would correspond to a 100% increase, which is likely to cause thyrotoxicosis.

👍 👎 Discuss (5) Improve

Next question

Pregnancy: thyroid problems

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

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Extended textbook

Links

Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

Score: **23.6%**

1 ✓
2 ✓

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Question 209 of 414 ✓

A 58-year-old man presents to the emergency department with chest pain and clamminess. An ECG demonstrates a suspected myocardial infarction and he is admitted for immediate treatment.

During the admission, blood tests and scores are performed to assess his risk factors:

Total cholesterol	4.8 mmol/L	(< 5)
Triglycerides	2.01 mmol/L	(< 2)
Cholesterol:HDL ratio	3.5	(< 5)
QRISK3 score	9%	(< 10)

What is the most appropriate management option?

Advise GP to recheck lipid profile in 3 months	10%
Advise GP to recheck lipid profile in 6 months	5%
Commence atorvastatin 20mg	13%
Commence atorvastatin 40mg	9%
Commence atorvastatin 80mg	62%

Patients with established cardiovascular disease (e.g. IHD, stroke, PVD) should take high-intensity statin therapy (e.g. atorvastatin 80mg) regardless of baseline lipid profile

Important for me Less important

NICE guidelines state that, irrespective of baseline lipid profile, high-intensity statin therapy should be prescribed for patients with established cardiovascular disease, including ischaemic heart disease, stroke and peripheral vascular disease. As this patient has experienced a myocardial infarction, he falls into this category. Even though his lipid blood tests are largely within normal ranges and his QRISK3 score (his risk of having a heart attack or stroke in the next 10 years) is under 10%, secondary prevention should be started - therefore, **commencing atorvastatin 80mg** is the correct option.

Advising the patient's GP to recheck lipid profile in 3 months is incorrect. As he now has established cardiovascular disease, commencing high-intensity statin therapy is optimal. If hyperlipidaemia had been found in the absence of established disease - that is, primary prevention was being considered - rechecking in 3 months may be appropriate if the patient wished to first try improving levels through diet and exercise.

Advising the patient's GP to recheck lipid profile in 6 months is incorrect. High-intensity statin therapy - atorvastatin 80mg - should be commenced. If this situation pertained to primary prevention (rather than established disease), rechecking lipids after 6 months may be an appropriate measure for a patient who wished to improve levels through diet and exercise rather than medication.

Commencing atorvastatin 20mg is incorrect. This is the dose used for primary prevention and is typically started for patients who have a QRISK3 score over 10%. It is an insufficient dose for secondary prevention - 80mg should be used here.

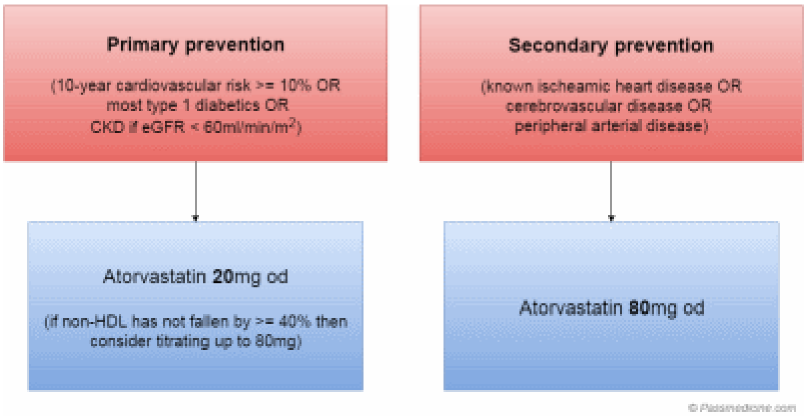
Commencing atorvastatin 40mg is incorrect. This dose is not recommended by NICE guidelines - it is between the primary and secondary prevention doses.

👍 👎 Discuss Improve

Next question

Hyperlipidaemia: management ★

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
    - older than 40 years, or
    - have had diabetes for more than 10 years or
    - have established nephropathy or
    - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months

- repeat a full lipid profile

- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet
- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity
- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management
- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake
- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation
- smokers should be encouraged to quit

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Question 210 of 414 ✗

A 55-year-old man with type 2 diabetes mellitus has his yearly health check-up at his GP surgery. His HbA1c is 86mmol/L and his GP is considering adding empagliflozin to help manage his diabetes.

HbA1c (mmol/L)	Interpretation
<42	Normal Glycaemic Control
42-47	Impaired Glucose Tolerance
>48	Diabetes Mellitus
86	Patient's Result

What is the mechanism of action of this medication?

	Blocks potassium channels on β islet cells in the pancreas	3%
🟩	Inhibition of the sodium-glucose transporter in the kidney	89%
	Inhibition of dipeptidyl peptidase 4	5%
	Inhibition of α glucosidase in the small intestine	1%
🟥	Stimulation of peroxisome proliferator-activated receptor	3%

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule

Important for me Less important

Empagliflozin is an SGLT-2 (sodium-glucose transport protein 2) inhibitor. These act in the proximal convoluted tubule of nephrons to inhibit glucose re-absorption back into the circulation by blocking SGLT-2 channels.

Sulphonylureas act via increasing insulin secretion from β islet cells in the pancreas. They do this via blockage of potassium channels, which causes islet cell depolarisation and release of insulin.

Inhibition of the enzyme DPP-4 (dipeptidyl peptidase 4) prevents the break down of GLP-1 (glucagon-like peptide), which in turn suppresses glucagon release and increases insulin release. Sitagliptin is an example of this class of drug.

Acarbose inhibits α glucosidase and other enzymes in the small intestine, preventing the breakdown of complex carbohydrates into glucose. As a result, less glucose is made available for absorption into the bloodstream.

Thiazolidinediones reduce insulin resistance in the peripheral tissues and decrease gluconeogenesis in the liver. They achieve this by stimulation of PPAR-Î^3 (peroxisome proliferator-activated receptor-gamma) which modulates the transcription of genes involved in glucose metabolism.

Discuss (1) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

B *I* A T↕

Textbooks

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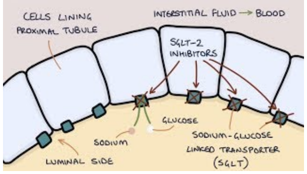
Links

BNF 👍 3 👎 9

Dapagliflozin

Report broken link

Media


CELLS LINING PROXIMAL TUBULE
INTERSTITIAL FLUID → BLOOD
SGLT-2 INHIBITORS
GLUCOSE
SODIUM
SODIUM-GLUCOSE LINKED TRANSPORTER (SGLT)
LUMINAL SIDE

How does Dapagliflozin work? Understanding SGLT2 inhibitors.

Zero To Finals - YouTube 👍 39 👎 2

Report broken media

Score: **23.8%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

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Question 211 of 414 ✗

A 66-year-old male reports he has noticed an increase in the amount of breast tissue he has which he finds embarrassing. He assures you that he has not put on weight. Further questioning reveals nothing of note.

His past medical history includes ischaemic heart disease, atrial fibrillation, prostate cancer and osteoarthritis of both hips. He takes atorvastatin, bisoprolol, goserelin, GTN spray, lansoprazole, naproxen and ramipril.

Which of his medications may account for his presenting complaint?

	Bisoprolol	3%
🟩	Goserelin	89%
	Lansoprazole	4%
🟥	Naproxen	1%
	Ramipril	3%

GnRH agonists (e.g. goserelin) used in the management of prostate cancer may result in gynaecomastia

Important for me Less important

The patient has presented with gynaecomastia. This is most likely due to taking goserelin for his prostate cancer. Goserelin is a GnRH agonist. It binds to the pituitary causing an increase in luteinising hormone, which in turn causes an increase in testosterone. After the initial flare, the negative feedback causing downregulation of the receptors in the pituitary and testosterone levels fall. The resultant change in oestrogen: androgen causes gynaecomastia.

Bisoprolol is a β-blocker and adverse effects include bronchospasm and bradycardia.

Lansoprazole is a proton pump inhibitor and adverse effects include hyponatraemia and hypomagnesaemia.

Naproxen is a non-steroidal anti-inflammatory drug. Adverse effects include worsening of asthma symptoms and upper gastrointestinal haemorrhage.

Ramipril is an ACE inhibitor and its most notable side effect is cough (due to bradykinin build up).

👍 | 👎 | Discuss (4) | Improve

Next question

Gynaecomastia ★

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin

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← Question 212 of 414 ✗ ⚐ →

A 40-year-old man presents to the GP concerned about his risk of developing cancer. You notice that he has large spade-like hands, a prominent forehead and nose, and thick skin. Which of the following cancers is he at increased risk of developing?

Pancreatic carcinoma	11%
🟩 Colorectal carcinoma	64%
Adrenal carcinoma	16%
Malignant melanoma	5%
🟥 Lung cancer	4%

Patients with acromegaly have an increased risk of colorectal carcinoma

Important for me Less important

Patients with acromegaly have an increased incidence of colorectal polyps and carcinoma. This is a fairly recent finding, now that patients with acromegaly are surviving longer due to better management of their other complications, particularly diabetes and cardiovascular disease. It is recommended that patients with acromegaly have an initial colonoscopy at age 40, and enter a surveillance program based on the results of the colonoscopy.

Guidelines for colorectal cancer screening and surveillance in moderate and high risks. Update https://www.ncbi.nlm.nih.gov/pubmed/20427401

Discuss (4) Improve

Next question

Acromegaly: features ★

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g.

pancreatic.

Features

- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin: caused by sweat gland hypertrophy
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea
- 6% of patients have MEN-1

Complications

- hypertension
- diabetes (>10%)
- cardiomyopathy
- colorectal cancer

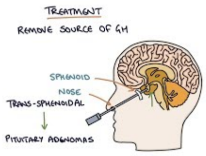
Next question

Textbooks

High-yield textbook

Extended textbook

Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 24 👎 1

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Question 213 of 414 ✗

A 72-year-old woman attends the clinic with a 6-month history of excessive thirst. She has a history of biventricular heart failure for which set takes ramipril, bisoprolol and furosemide.

Blood results are as follows:

Hb	124 g/L	Male: (135-180) Female: (115 - 160)
Platelets	158 * 10^9/L	(150 - 400)
WBC	8.4 * 10^9/L	(4.0 - 11.0)
Na^+	135 mmol/L	(135 - 145)
K^+	3.6 mmol/L	(3.5 - 5.0)
Urea	9.6 mmol/L	(2.0 - 7.0)
Creatinine	146 µmol/L	(55 - 120)
CRP	2 mg/L	(< 5)

Calcium	2.85 mmol/L	(2.1-2.6)
Phosphate	0.62 mmol/L	(0.8-1.4)
PTH	4.8 pmol/L	(1.6 - 6.9)

What is the most likely cause?

Furosemide	14%
Osteopenia	3%
Primary hyperparathyroidism	50%
Secondary hyperparathyroidism	20%
Tertiary hyperparathyroidism	13%

The PTH level in primary hyperparathyroidism may be normal

Important for me Less important

Primary hyperparathyroidism is correct. This condition is characterised by hypercalcaemia with a raised or inappropriately normal PTH. The PTH levels are generally elevated in primary hyperparathyroidism, although approximately 10% to 20% of individuals will have 'inappropriately normal' levels. Renal impairment is commonly seen in patients with hypercalcemia primarily as a consequence of dehydration.

Furosemide is incorrect. Furosemide is a loop diuretic agent that can be used to treat hypercalcemia because it increases renal calcium excretion.

Osteopenia is incorrect. This is a quantitative, not qualitative, disorder of bone mineralisation. Laboratory bone profile results are usually normal, and the diagnosis relies on a DEXA scan.

Secondary hyperparathyroidism is incorrect. This occurs as the physiological response to hypocalcemia. Kidney failure and vitamin D deficiency are the most common causes of secondary hyperparathyroidism. The key biochemical features are hypocalcemia and a raised PTH. A raised ALP also occurs due to excessive bone resorption. Phosphate levels will vary with aetiology e.g. raised in kidney failure and decreased in vitamin D deficiency.

Tertiary hyperparathyroidism is incorrect. This occurs when an excess of PTH is secreted by the parathyroid glands, usually after longstanding secondary hyperparathyroidism results in hyperplasia of the parathyroid glands. It biochemically presents the same as primary hyperparathyroidism with raised calcium and elevated PTH. Although this remains a possibility, the patient only has mild renal impairment making this a less likely diagnosis. Furthermore, the phosphate level would generally be high in tertiary hyperparathyroidism (due to reduced renal clearance).

Discuss (2) Improve

Next question

Primary hyperparathyroidism

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma

- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':

- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations

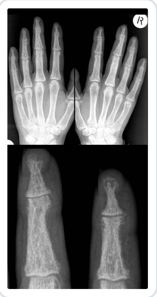
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- bloods
  - raised calcium, low phosphate
  - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
  - pepperpot skull
  - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
  - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



Next question

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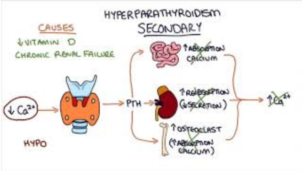
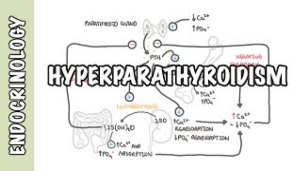

HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
PTH
HYPO
↑Ca2+

Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2

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← Question 214 of 414 ✗ →

A 25-year-old woman presents for her first cervical smear. What is the most important aetiological factor causing cervical cancer?

Human papilloma virus 6 & 11	8%
Herpes simplex virus 2	0%
Smoking	20%
Combined oral contraceptive pill use	1%
Human papilloma virus 16 & 18	71%

Cervical cancer: Human papillomavirus infection (particularly 16,18 & 33) is by far the most important risk factor

Important for me Less important

Whilst a number of the above are known to contribute to the development of cervical cancer infection with human papilloma virus 16 & 18 is by far the most important factor.

Discuss (5) Improve

Next question

Cervical cancer ★

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. It may be divided into:

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papillomavirus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov 10;370(9599):1609-21) confirmed the link

Next question

Textbooks

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Extended textbook

Links

Cancer Research UK 👍 0 👎 0

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← Question 215 of 414 ✓ →

A 50 year-old woman presents with polyuria and polydipsia. She has recently been started on citalopram for depression, but is otherwise fit and well. She has complained of constipation recently, but has put this down to her new medication.

Calcium	2.8mmol/l
Phosphate	0.7mmol/l
Parathyroid hormone	5.0pmol/l (1.2-5.8pmol/l)

Renal function and full blood count are normal.

What is the most likely cause for these blood results?

Parathyroid adenoma	41%
Myeloma	4%
Metastatic cancer	7%
Drug induced	29%
Parathyroid hyperplasia	18%

The PTH level in primary hyperparathyroidism may be normal

Important for me Less important

This woman has signs and symptoms of hypercalcaemia. Her parathyroid hormone should be suppressed in the presence of hypercalcaemia. Given that it is normal (inappropriately), this indicates the parathyroid as the cause for the hypercalcaemia. The most common cause of hyperparathyroidism is an adenoma.

Discuss (7) Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

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- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations
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- x-ray findings
  - pepperpot skull
  - osteitis fibrosa cystica

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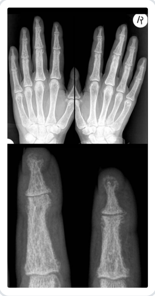
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



Next question

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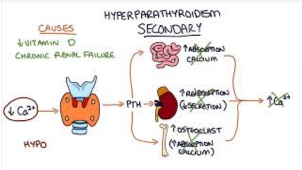
HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓ VITAMIN D
CHRONIC RENAL FAILURE
↓ Ca²⁺
HYPO
PTH
↑ ABSORPTION CALCIUM
↑ REABSORPTION (↓ SECRETION)
↑ OSTEOCLAST (↑ ABSORPTION CALCIUM)
↑ Ca²⁺

Understanding Hyperparathyroidism

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70 2

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← Question 216 of 414 × →

A 25-year-old man presents to endocrinology clinic for review. He has been referred with a sodium of 130mmol/L. He feels well in himself and denies any systemic symptoms and specifically has no headaches or neurological symptoms. He has been passing normal volumes of urine. He has a past medical history of familial hypercholesterolemia and is under review by a metabolic team as he still has a total cholesterol of 9.1mmol/L. Paired osmolalities are normal. Urine dipstick test is normal. His examination is largely normal apart from evidence of xanthomas. U&E, FBC, LFTs are normal. What is the most likely diagnosis?

🟩	Pseudohyponatraemia	88%
	Nephrogenic SIADH	4%
🟥	Cranial SIADH	3%
	Diabetes insipidus	2%
	Type two diabetes mellitus	3%

The correct answer is pseudo hyponatraemia. This is a patient with clinical and biochemical evidence of very high cholesterol levels in addition to his mild hyponatraemia. The normally paired osmolalities exclude SIADH and diabetes insipidus, whilst the absence of glucosuria makes diabetes an unlikely cause.

👍 👎 Discuss (6) Improve

Next question

Hyponatraemia ★

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis

Urinary sodium > 20 mmol/l

Sodium depletion, renal loss (patient often hypovolaemic)

- diuretics: thiazides, loop diuretics
- Addison's disease
- diuretic stage of renal failure

Patient often euvolaemic

- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

Urinary sodium < 20 mmol/l

Sodium depletion, extra-renal loss

- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)

- secondary hyperaldosteronism: heart failure, liver cirrhosis
- nephrotic syndrome
- IV dextrose
- psychogenic polydipsia

Next question

Textbooks

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Links

Royal College of Physicians 👍 5 👎 2

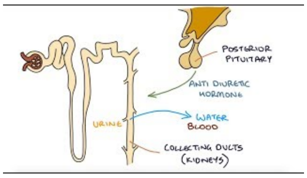
2017 Hyponatraemia â€“ presentations and management

European Society of Endocrinology 👍 6 👎 4

2014 Guidelines on diagnosis and treatment of hyponatraemia

Report broken link

Media


POSTERIOR PITUITARY
ANTI DIURETIC HORMONE
URINE
WATER
BLOOD
COLLECTING DUCTS (KIDNEYS)

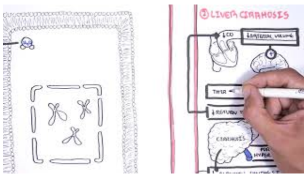
Understanding Hyponatraemia

Zero To Finals - YouTube 👍 68 👎 3

WHAT IS...
SIADH?

Syndrome of inappropriate antidiuretic hormone (SIADH)

Osmosis - YouTube 👍 9 👎 2


LIVER CIRRHOSIS

Hyponatraemia - classification, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 8 👎 2

Report broken media

PassMedicine

Question 217 of 414 ✗

A previously well 42-year-old man is referred to the renal team for further investigation following admission for recurrent renal colic. This is the patient's third presentation with renal stones over the last few months and a CT performed demonstrated extensive bilateral kidney stones.

The patient was initially admitted as basic investigations performed within the emergency department on presentation found he had a significant metabolic acidosis, with a normal anion gap, as well as hypokalaemia.

What form of renal acid accumulation does this patient most likely have?

Fanconi syndrome	5%
Lightwood-Albright syndrome	1%
🟩 Type 1 renal tubular acidosis	76%
Type 2 renal tubular acidosis	13%
🟥 Type 4 renal tubular acidosis	4%

Type 1 renal tubular acidosis (distal) complication - renal stones

Important for me Less important

This patient has presented with the characteristic features of **type 1 renal tubular acidosis** with hypokalaemia, metabolic acidaemia (with a normal anion gap) and, unlike in other forms of the condition, renal stones. In type 1 renal tubular acidosis (RTA) it is the distal aspect of the nephrons (distal tubules) that are dysfunctional and fail to secretion H+ ions into the urine. As this is one of the primary means of removing H+ ions from the body there is a resultant decreased pH of the blood (metabolic acidaemia) as well as an increased pH of the urine (alkaline). Calcium phosphate stones (the most common cause of renal stones) have an increased tendency to be deposited at higher pHs and therefore bilaterally renal calci are commonly associated with this type of RTA; this does not occur in the other forms of the condition.

Fanconi syndrome is associated with inadequate proximal renal tubule reabsorption resulting in the loss of ions such as bicarbonate (the main feature of type 2 RTA) and phosphate. It may be caused by several congenital or acquired conductions as well as a complication of certain medication use. This failure of bicarbonate reabsorption, and therefore bicarbonate wasting into the urine, is what subsequently results in acidaemia. As the main feature of Fanconi syndrome is that of proximal rental tubule dysfunction it is associated with type 2 renal tubular acidosis (not type 1 which is associated with distal tubular dysfunction) and therefore not renal stones.

Lightwood-Albright syndrome is a neonatal form of RTA with a known genetic inheritance pattern. Affected children present early in life with complications and therefore would not present as an index case in adulthood, as in this case.

Type 2 renal tubular acidosis as mentioned is a result of proximal renal tubule dysfunction with inadequate reabsorption of filtered bicarbonate. As the distal aspect of the nephrons still function as normal in type 2 RTA, the acidaemia is less severe and H+ ions can be secreted into the urine therefore acidifying it. As the urine is not alkali there is not an associated increased deposit of calcium phosphates or the formation of renal stones.

Type 4 renal tubular acidosis is not actually a tubular/nephron disorder and is unlikely the other syndrome described. Instead, it is due to either aldosterone deficiency or resistance. Type 4 RTA was originally included in the RTA classification as it is associated with a mild (normal anion gap) metabolic acidosis due to a reduction in proximal tubular ammonium excretion, secondary to this hypoaldosteronism. As such it is not associated with renal stones.

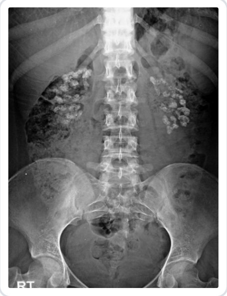
👍 👎 💬 Discuss (4) Improve

Next question

Renal tubular acidosis ★

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)
- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

Textbooks

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Question 218 of 414 ✗

A 53-year-old male presents to the Emergency Department complaining of extreme fatigue. He has a background of treated Graves disease. On examination his blood pressure is 103/58 mmHg, pulse 64/min and temperature 36.3°C. The following results are obtained:

Na+	135 mmol/l
K+	5.4 mmol/l
Urea	5.2 mmol/l
Creatinine	42 umol/l
TSH	3.5 mu/l
Free thyroxine (T4)	12 pmol/l

You arrange for a random cortisol test however whilst awaiting the result he becomes unresponsive. In addition to giving intravenous steroid and fluid, what test is it imperative to check first given the likely diagnosis?

	Serum calcium	9%
	ECG	16%
🟥	Arterial pH	9%
	Prolactin	2%
🟩	Glucose	65%

This question is alluding to a diagnosis of Addison's disease. The autoimmune history, raised potassium, fatigue and low blood pressure are all clues to this.

Patients with Addison's disease are prone to developing hypoglycaemia due to loss of the glucogenic effect of glucocorticoids. Given the sudden deterioration in GCS, a glucose level must be checked.

Addison's disease:
Addison's is adrenocortical insufficiency due to the dysfunction/destruction of the adrenal cortex. It affects both glucocorticoid (metabolism of glucose etc.) and mineralocorticoid (salt balance)

function. The commonest cause in the developed world is autoimmune adrenalitis. Other causes include destruction of the cortex by infections such as TB, or metastasis.

Signs/symptoms of Addisonian crisis:

Neurological
- syncope
- confusion
- lethargy
- convulsions

Haemodynamic
- hypotension
- hypothermia

Biochemical
- hyponatraemia
- hyperkalaemia
- hypoglycaemia

Management of Addisonian crisis (medical emergency):
- intravenous fluids
- corticosteroids (e.g iv dexamethasone)

Note: iv dexamethasone is often preferred as this will not interfere with cortisol assays needed for a short synacthen test, unlike hydrocortisone.

👍 👎 Discuss (10) Improve

Next question

Addisonian crisis ★

Causes
- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococcemia)
- steroid withdrawal

Management

- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

Next question

Textbooks

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Extended textbook

Links

Royal College of Physicians 👍 2 👎 1

2017 Adrenal insufficiency â€“ recognition and management

Report broken link

Media

ADDISON'S DISEASE

Addison's disease

Armando Hasudungan - YouTube 👍 4 👎 1

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Question 219 of 414 ✗

A 53-year-old man with a history of type 2 diabetes mellitus is reviewed in the diabetes clinic. Twelve months ago his HbA1c was 83 mmol/mol (9.7%) despite maximal oral hypoglycaemic therapy. Insulin was started and his most recent HbA1c is 66 mmol/mol (8.2%). He is considering applying for a HGV licence and asks for advice. What is the most appropriate advice?

	He cannot drive a heavy goods vehicle if he is taking insulin	19%
🟩	He may be able to apply for a HGV licence if he meets strict criteria relating to hypoglycaemia	65%
🟥	He should stop insulin and start meglitinide	3%
	As under 55 years of age there is no requirement to inform the DVLA	5%
	He needs to have been stable on insulin for at least 5 years before applying	9%

Patients on insulin may now hold a HGV licence if they meet strict DVLA criteria

Important for me Less important

The most appropriate advice for this patient is that **he may be able to apply for a HGV licence if he meets strict criteria relating to hypoglycaemia**. According to the UK Driver and Vehicle Licensing Agency (DVLA), people with insulin-treated diabetes can apply for a group 2 (lorry or bus) driving licence if they have no episodes of severe hypoglycaemia within the last 12 months, have full awareness of hypoglycaemia, and can show adequate blood glucose monitoring. The patient would need to demonstrate good control of their diabetes and meet these requirements in order to be eligible.

The option stating **he cannot drive a heavy goods vehicle if he is taking insulin** is incorrect. As mentioned above, it is possible for an individual on insulin therapy to obtain a HGV licence provided they meet certain criteria.

The suggestion that **he should stop insulin and start meglitinide** is not appropriate. Meglitinides are short-acting oral antidiabetic agents that stimulate insulin secretion; however, they are not recommended as an alternative to insulin therapy in patients with type 2 diabetes who require insulin due to inadequate glycaemic control with oral medications.

The statement that **as under 55 years of age there is no requirement to inform the DVLA** is incorrect. Age does not play a role in determining whether someone needs to inform the DVLA about their medical condition. All drivers with insulin-treated diabetes are required by law to notify the DVLA regardless of their age.

Lastly, the claim that **he needs to have been stable on insulin for at least 5 years before applying** is also incorrect. There is no specific duration of stability on insulin required by the DVLA before applying for a group 2 driving licence. The primary concern relates to adequate blood glucose monitoring and the absence of severe hypoglycaemic episodes within the past 12 months.

👍 👎 Discuss (1) Improve

Next question

DVLA: diabetes mellitus ★

Until recently people with diabetes who used insulin could not hold a HGV licence. The DVLA changed the rules in October 2011. The following standards need to be met (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):

- there has not been any severe hypoglycaemic event in the previous 12 months
- the driver has full hypoglycaemic awareness
- the driver must show adequate control of the condition by regular blood glucose monitoring*, at least twice daily and at times relevant to driving
- the driver must demonstrate an understanding of the risks of hypoglycaemia
- here are no other debarring complications of diabetes

From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) licence need to complete a VDIAB1I form.

Other specific points for group 1 drivers:

- if on insulin then patient can drive a car as long as they have hypoglycaemic awareness, not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months and no relevant visual impairment. Drivers are normally contacted by DVLA
- if on tablets or exenatide no need to notify DVLA. If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- if diet controlled alone then no requirement to inform DVLA

*to demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that applicants will need to have used blood glucose meters with a memory function to measure and record blood glucose levels for at least 3 months prior to submitting their application

Next question

Textbooks

High-yield textbook

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Links

Gov.uk 👍 1 👎 1

Diabetes and driving

DVLA 👍 0 👎 1

Fitness to drive guidelines

Report broken link

Score: **23.3%**

1 ✓

2 ✓

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Question 220 of 414 ✓

A 52-year-old woman with suspected diabetes mellitus has an oral glucose tolerance test, following the standard WHO protocol. The following results are obtained:

Time (hours)	Blood glucose (mmol/l)
0	5.9
2	8.4

How should these results be interpreted?

Impaired fasting glucose and impaired glucose tolerance	11%
Normal	18%
Diabetes mellitus	9%
[✓ Impaired glucose tolerance]	59%
Impaired fasting glucose	4%

Discuss (7) Improve

Next question

Diabetes mellitus (type 2): diagnosis

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic: CKS

- fasting glucose greater than or equal to 7.0 mmol/l

- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

When HbA1c is used for the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis: **CKS**

- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

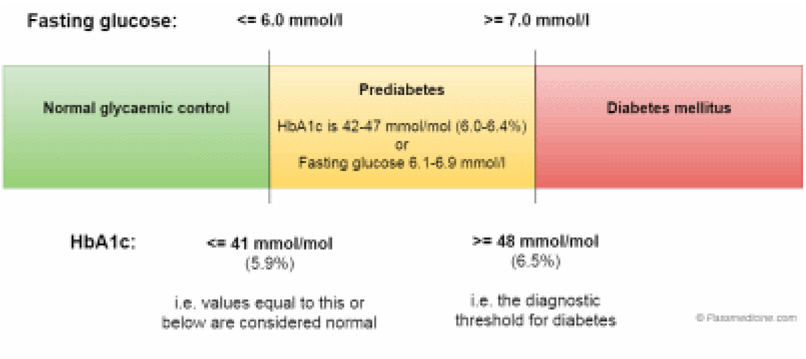
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
© Passmedicine.com

Diagram showing the spectrum of diabetes diagnosis

Impaired fasting glucose and impaired glucose tolerance

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:

- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 2 👎 1

Type 2 diabetes mellitus: diagnosis

NICE 👍 2 👎 2

2022 Type 2 diabetes guidelines

Diabetes UK 👍 3 👎 4

New diagnostic criteria for diabetes

Report broken link

Media

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← Question 221 of 414 ✓ →

A 48-year-old man with obesity and hypertension is brought to the emergency department by his concerned wife due to confusion, vomiting, and abdominal pain. She has long struggled to persuade him to seek medical care due to his medication non-compliance.

He was found to be in a hyperosmolar hyperglycaemic state, a complication of previously undiagnosed diabetes, and following initial management is initiated on an antidiabetic medication that targets ATP-dependent K+ channels on pancreatic beta cells. This drug is preferable to him over insulin injections.

What class of drug has he been commenced on?

Biguanide	24%
Dipeptidyl peptidase-4 inhibitor	10%
[✓ Meglitinides]	50%
Sodium/glucose cotransporter 2	7%
Thiazolidinediones	9%

Meglitinides - bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells

Important for me Less important

Meglitinides such as repaglinide and nateglinide, are a class of oral antidiabetic medications primarily used in diabetic patients with type 2 diabetes. They work by stimulating the release of insulin from the pancreas in response to meal consumption. This mechanism of action involves targeting ATP-dependent K+ channels on pancreatic beta cells, helping control blood sugar levels after eating. Meglitinides are particularly suitable for individuals with irregular eating patterns or those who cannot tolerate other diabetes medications, offering flexibility in timing as they are taken just before meals, making them a valuable option for patients who require better post-meal glucose control.

Biguanides, a group of oral antidiabetic drugs frequently prescribed to individuals with type 2 diabetes, include notable examples such as metformin. Their primary mode of action involves reducing liver glucose production and enhancing muscle cell responsiveness to insulin, leading to better blood sugar regulation and reduced fasting glucose levels. While the exact pharmacokinetics of biguanides remain unknown, there is no evidence to suggest that they specifically target pancreatic beta cells.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antidiabetic medications commonly prescribed for individuals with type 2 diabetes. Examples include sitagliptin, saxagliptin, and linagliptin. These medications work by inhibiting the enzyme DPP-4, which inactivates incretin hormones such as GLP-1 and GIP. By blocking DPP-4, these inhibitors extend the action of incretin hormones, resulting in increased insulin release and reduced glucagon secretion from the pancreas. This helps lower blood sugar levels, especially after meals.

Sodium/glucose cotransporter 2 (SGLT2) inhibitors are a class of oral antidiabetic medications typically prescribed for patients with type 2 diabetes. Notable examples include empagliflozin, dapagliflozin, and canagliflozin. The primary mechanism of action of SGLT2 inhibitors is to block the SGLT2 protein in the kidneys. This prevents the reabsorption of glucose from the urine back into the bloodstream, leading to increased urinary glucose excretion. By reducing blood sugar levels in this manner, these drugs help lower overall glucose levels in diabetic individuals.

Thiazolidinediones (TZDs) are a class of oral antidiabetic medications commonly prescribed for individuals with type 2 diabetes. Examples include pioglitazone and rosiglitazone. The primary mechanism of action of TZDs involves improving insulin sensitivity in peripheral tissues, such as muscle and fat cells. They activate peroxisome proliferator-activated receptor-gamma (PPAR-Î³) receptors, which regulate genes related to glucose and lipid metabolism. This results in enhanced insulin action and better blood sugar control.

👍 👎 Discuss Improve

Next question

Meglitinides

Meglitinides (e.g. repaglinide, nateglinide)

- increase pancreatic insulin secretion
- like sulfonylureas they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells
- often used for patients with an erratic lifestyle
- adverse effects include weight gain and hypoglycaemia (less so than sulfonylureas)

Next question

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Question 222 of 414

A 48-year-old woman presents to her general practitioner with longstanding menorrhagia. Her periods are regular but increasingly heavy. Her past medical history includes hypertension, hypothyroidism and asthma, for which she takes ramipril, amlodipine, levothyroxine, montelukast and a beclometasone inhaler - all in the morning. Examination and observations are normal. Blood tests are performed, which show mild iron-deficiency anaemia; she is commenced on ferrous sulfate once daily.

What advice should she be given regarding the new medication?

Take at least 1 hour after current morning tablets	6%
Take at least 2 hours after current morning tablets	10%
Take at least 4 hours after current morning tablets	74%
Take just after eating food	8%
Take with current morning tablets	1%

Iron / calcium carbonate tablets can reduce the absorption of levothyroxine - should be given 4 hours apart

Important for me Less important

Administration of ferrous sulfate or ferrous fumarate is a very common initial treatment plan for iron-deficiency anaemia. The full blood count is then typically rechecked within a few weeks, and again after several months. It is important to be aware of the patient's other medications, as ferrous compounds can interact with several drugs. Of note, iron tablets can reduce the absorption of levothyroxine. Manufacturer and BNF guidance states that any iron tablets should be given **at least 4 hours** apart from levothyroxine.

Giving after just **1 hour** is therefore incorrect - this is insufficient and may affect the absorption of levothyroxine.

Similarly, giving after **2 hours** is also insufficient.

Taking just after eating food is not recommended. Iron is best absorbed on an empty stomach.

Advising her to take the iron tablet **with her current morning tablets** is incorrect, as it will interfere with levothyroxine. If she did not have hypothyroidism, taking iron in the morning alongside the remaining medications would be fine.

👍 👎 Discuss (1) Improve

Next question

Hypothyroidism: levothyroxine therapy ★

Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value
- there is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions

- iron, calcium carbonate
  - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

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Question 223 of 414 ✗ ⚐

A 43-year-old man presents to his GP with tiredness, low mood and unintentional weight gain of 13kg over the past 4 months. Prior to feeling like this he recalls having a flu-like illness following which he had a two-week period of feeling very anxious, shaky and energetic. He wonders if this is connected.

On examination he has a heart rate of 68 bpm, his blood pressure is 147/83 mmHg and his temperature is 37.1ºC. Examination of his abdomen and chest are unremarkable and he does not have a goitre or any palpable lymphadenopathy. He has no family history of note and no past medical history.

Blood tests to look at his thyroid function show the following:

Thyroid stimulating hormone (TSH)	6.1 mu/l	(0.5-5.5 mu/l)
Free T4	6 pmol/l	(9-18 pmol/l)

What is the most likely cause of this man's symptoms?

	Grave's disease	2%
🟥	Hashimoto's thyroiditis	32%
	Papillary cancer of the thyroid	1%
🟩	De Quervain's thyroiditis	64%
	Toxic multinodular goitre	1%

Subacute thyroiditis causes hyper- then hypothyroidism

Important for me Less important

This gentleman has a clinical picture of hypothyroidism with what appears to be a brief period of hyperthyroidism prior to this. The most common cause of this is De Quervain's thyroiditis and this would be in keeping with the history of a viral infection before the initial hyperthyroid episode. There is a rare form of Hashimoto's in which the patient has an initial phase of hyperthyroidism before becoming hypothyroid, however the period of hyperthyroidism is prolonged in those cases and the clinical picture is often indistinguishable from Grave's disease. In addition it happens far more commonly in women than men (around 5 times) and has a strong association with other auto-immune diseases. The key to this question is what is most likely and given the relatively brief period of hyperthyroidism (in Hashimoto's it would be in the order of 6-12 months rather than a few weeks) and the preceding viral infection, De Quervain's is far more likely.

Grave's disease and toxic multinodular goitre would both present with hyperthyroidism and papillary thyroid cancer does not produce thyroxine so would not cause any systemic symptoms.

👍 👎 Discuss (9) Improve

Next question

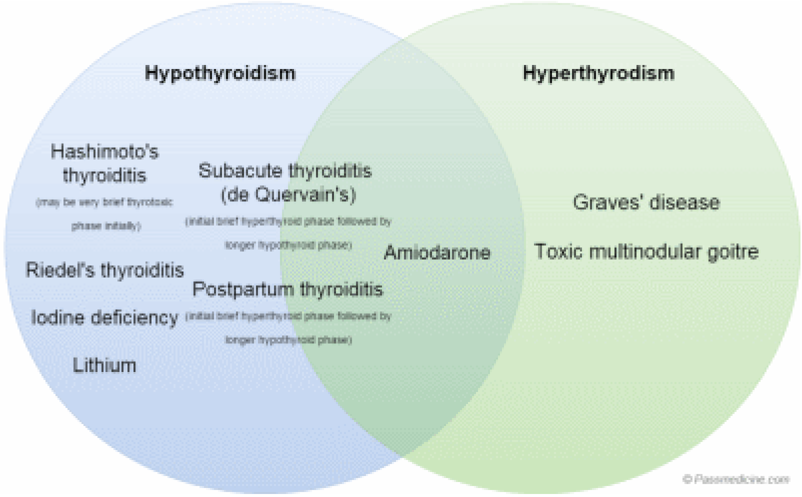
Subacute (De Quervain's) thyroiditis

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

Investigations
- thyroid scintigraphy: globally reduced uptake of iodine-131

Management
- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
Amiodarone
Graves' disease
Toxic multinodular goitre
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Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

Textbooks

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Score: **23.8%**

1 ✓
2 ✓
3 ✓
4 ✗

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← Question 224 of 414 ✕ →

A 40-year-old man is admitted after sustaining a femur fracture following a fall. He has undergone a thyroidectomy previously for medullary thyroid cancer, which he reports runs in the family. On enquiry, he admits that he has frequent headaches associated with sweating and palpitations. His blood pressure readings are persistently high, with a systolic pressure ranging from 150 to 160 mmHg and diastolic pressure 100 to 110 mmHg. A 24-hour urine metanephrine test is performed and is reported as positive.

What genetic mutation is most likely to underlie the diagnosis?

	MEN1 oncogene	31%
	NF1 gene	3%
🟩	RET oncogene	63%
🟥	TSC1 gene	1%
	VHL gene	3%

Medullary thyroid cancer is associated with the RET oncogene

Important for me Less important

The correct answer is **RET oncogene**. The patient's history of medullary thyroid cancer, which is familial, and symptoms suggestive of phaeochromocytoma (headaches, sweating, palpitations, and hypertension) indicate a diagnosis of Multiple Endocrine Neoplasia (MEN) type II. This condition is associated with mutations in the RET oncogene. MEN type II has two subtypes: MEN IIA and MEN IIB. Both are associated with medullary thyroid cancer and phaeochromocytoma. MEN IIA also includes parathyroid hyperplasia or adenomas, whereas MEN IIB includes mucosal neuromas and a marfanoid habitus.

MEN 1 is incorrect, as this gene mutation is responsible for developing MEN1 syndrome, which is characterised by an inherited predisposition to developing pituitary, parathyroid gland and pancreatic islet cell tumours. It is inherited in an autosomal dominant fashion. This patient has a history of medullary thyroid cancer, which makes MEN1 unlikely.

NF1 gene mutation is incorrect, as this mutation results in neurofibromatosis type 1, which is an autosomal dominant genetic disorder characterised by cafe-au-lait macules, axillary freckling, Lisch nodules (iris hamartomas) and neurofibromas. In this case, the absence of these clinical features prompts consideration of other differentials.

TSC1 gene mutation is incorrect. This mutation is implicated in the development of tuberous sclerosis, an autosomal dominant disorder that leads to multiple hamartomas in the brain, eyes, lung, heart, liver, kidney and skin. Skin manifestations of note include shagreen patch, subungual fibromas and hypomelanotic macules. The clinical features in the case provided do not match the characteristics of tuberous sclerosis.

VHL gene is incorrect. The VHL gene is responsible for the Von Hippel-Lindau disease (VHL) development. VHL disease is inherited in an autosomal dominant fashion. Brain and spinal cord hemangioblastomas, retinal angiomas, clear cell renal cell carcinoma and some other tumours characterise this. These patients do have a higher risk of developing phaeochromocytomas. However, considering the patient in this clinical scenario had a history of medullary thyroid cancer, VHL disease is unlikely.

👍 👎 💬 Discuss Improve

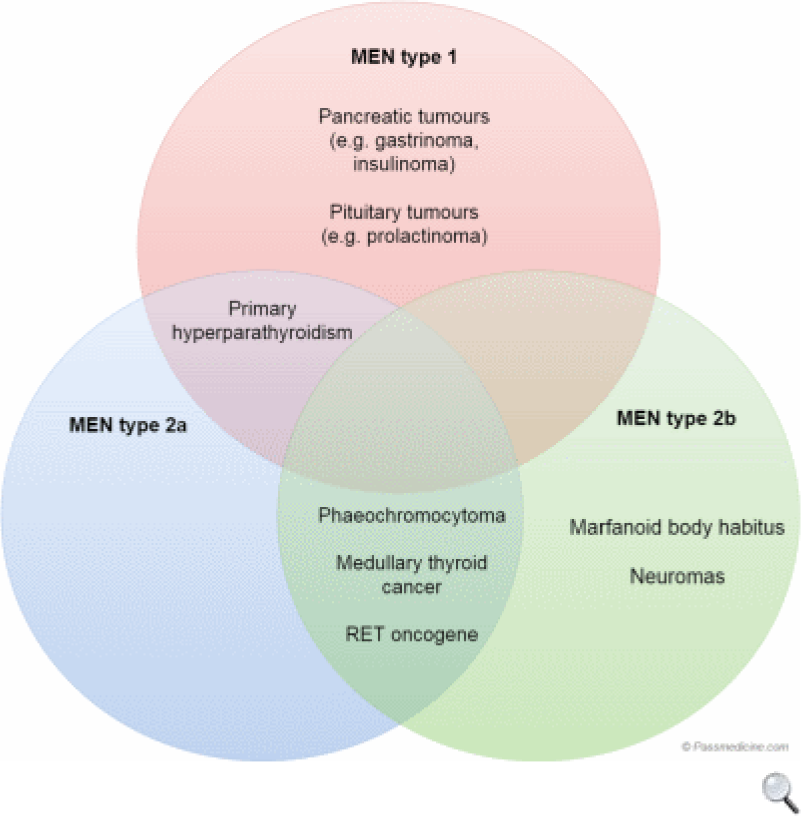
Next question

Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	Medullary thyroid cancer 1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas

MEN type I	**MEN type IIa**	**MEN type IIb**
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
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Venn diagram showing the different types of MEN and their associated features

Next question

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Question 225 of 414 ✗

A 48-year-old man presents to his GP with a 3-year history of hypertension that has been difficult to bring under control. No medication has been successful in reducing his blood pressure significantly. Accompanying the high blood pressure are muscle weakness and nocturia.

On examination, his blood pressure is 164/82 mmHg. Blood tests demonstrate low potassium and high aldosterone-to-renin ratio.

Given the likely diagnosis, which of the following is the most likely cause of this patient's presentation?

	Adrenal adenoma	15%
🟥	Adrenocortical carcinoma	2%
🟩	Bilateral idiopathic adrenal hyperplasia	76%
	Ectopic aldosterone-producing adenoma	5%
	Unilateral adrenal hyperplasia	2%

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Important for me Less important

The history and examination findings indicate primary hyperaldosteronism, which is the most common cause of primary hypertension. The most common cause of primary hyperaldosteronism is bilateral idiopathic adrenal hyperplasia - approximately two-thirds of cases. Classically, the presentation includes hypokalaemia, but in reality, most patients have normal potassium levels.

An adrenal adenoma is incorrect - this was previously thought to be the most common cause. However, bilateral idiopathic adrenal hyperplasia is actually far more common, with adrenal adenomas counting towards just 33% of cases.

Adrenocortical carcinoma is a rare cause of primary hyperaldosteronism - <1% of all cases.

Ectopic aldosterone-producing adenomas are another rare cause - <0.1% of all cases.

Unilateral adrenal hyperplasia is also less common than bilateral idiopathic adrenal hyperplasia - only accounting for approximately 2% of all cases.

👍 👎 💬 Discuss (2) Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes

- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

Features

- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

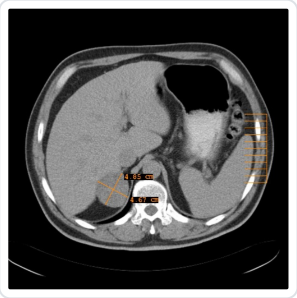
Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)

- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
    - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



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Links

The Endocrine Society 👍 5 👎 3

2016: The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment

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Question 226 of 414 ✗

A 43-year-old man is found to have a phaeochromocytoma. Which anti-hypertensive medication should be started first?

Propranolol	10%
Ramipril	6%
Atenolol	4%
Phenoxybenzamine	57%
Doxazosin	23%

PHaeochromocytoma - give **PH**enoxybenzamine before beta-blockers

Important for me Less important

Phenoxybenzamine is a non-selective alpha-adrenoceptor antagonist and should be started before a beta-blocker is introduced

There is ongoing debate about the optimal medical management of phaeochromocytoma, with the suggestion that antihypertensive treatment regimes other than non specific alpha-blockade are just as effective and safe. There are however no trials to provide an answer to this question yet

Discuss (3) Improve

Next question

Phaeochromocytoma

Phaeochromocytoma is a rare catecholamine secreting tumour. About 10% are familial and may be associated with MEN type II, neurofibromatosis and von Hippel-Lindau syndrome

Basics

- bilateral in 10%

- malignant in 10%
- extra-adrenal in 10% (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)

Features are typically episodic

- hypertension (around 90% of cases, may be sustained)
- headaches
- palpitations
- sweating
- anxiety

Tests

- 24 hr urinary collection of metanephrines (sensitivity 97%*)
- this has replaced a 24 hr urinary collection of catecholamines (sensitivity 86%)

Surgery is the definitive management. The patient must first however be stabilized with medical management:

- alpha-blocker (e.g. phenoxybenzamine), given before a
- beta-blocker (e.g. propranolol)

*BMJ 2012; 344 doi: http://dx.doi.org/10.1136/bmj.e1042 (Published 20 February 2012)

Next question

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Question 227 of 414 ✗

A 45-year-old male is investigated for polyuria. A water deprivation test is done to ascertain the cause.

Water deprivation began at 8 am.

Plasma osmolality after 8 hours	297 mOsm/kg
Urine osmolality after 8 hours	802 mOsm/kg

What is the next appropriate step in investigation or management?

	Continue with desmopressin administration	26%
	Give intravenous 0.9% sodium chloride as plasma osmolality is dangerously high	3%
🟥	Stop the test as plasma osmolality is dangerously high	3%
	Stop the test as results suggest diabetes insipidus	15%
🟩	Stop the test as results suggest primary polydipsia	53%

Water deprivation test: primary polydipsia

- urine osmolality after fluid deprivation: high
- urine osmolality after desmopressin: high

Important for me Less important

This is a case of primary polydipsia. After 8 hours of water deprivation, a distinction can be made as to whether the patient has diabetes insipidus (of either cause) or primary polydipsia based on urine osmolality alone.

If the urine osmolality is above 800 mOsm/kg, then the patient does not have diabetes insipidus (DI) and in fact, is considered diagnostic for primary polydipsia.

Now to look at the other options.

Continue with desmopressin administration - incorrect as DI is excluded when the urine osmolality is that high.

Give intravenous 0.9% sodium chloride as plasma osmolality is dangerously high - again incorrect. It would be unusual for a patient to need IV fluids as they should have a thirst response kick in first. Based on the study below, the maximum serum osmolality a patient reached was 311 mOsm/kg. If their neurological status changed or they became unstable, these would be reasons to abandon the test and treat the patient.

Stop the test as plasma osmolality is dangerously high - incorrect as whilst this is on the higher end of normal, this is to be expected during a water deprivation test. Provided the patient hasn't lost a significant amount of body weight (between 2-3% of body weight is usual), then it is safe to continue. If they have lost over 3% or they have debilitating side effects, you should review the patient to see if the test needs to be stopped.

Stop as the results suggest diabetes insipidus - incorrect as the results are suggestive of polydipsia. The urine osmolality is often below 300 mOsm/kg, however, you wouldn't stop here if you suspect DI. You would need to establish the origin of the pathology given the influence it has on management.

Diagnostic value of the water deprivation test in the polyuria-polydipsia syndrome. Trimpou et al. HORMONES 2017, 16(4):414-422.

Discuss (5) Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

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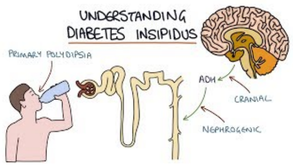
UNDERSTANDING
DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

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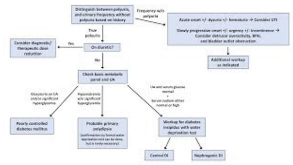

An Approach to Polyuria

Strong Medicine - YouTube

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Question 228 of 414

A 66-year-old man presented with several months of epigastric discomfort, anorexia and weight loss. His past medical history includes gastroesophageal reflux disease, Hashimoto's autoimmune thyroiditis, and type 2 diabetes mellitus. He is a current smoker and alcoholic. An endoscopy was performed and a suspicious lesion was biopsied from the stomach. The histology report confirmed the diagnosis of mucosa-associated lymphoid tissue (MALT) lymphoma.

What risk factor does he have for developing this condition?

Alcoholism	2%
Current smoker	7%
Gastro-oesophageal reflux disease (GORD)	12%
Hashimoto's thyroiditis	76%
Type 2 diabetes mellitus	2%

Hashimoto's thyroiditis is associated with the development of MALT lymphoma

Important for me Less important

Research shows **Hashimoto's thyroiditis** is amongst the autoimmune diseases found to be associated with the development of MALT lymphomas. Current theories suggest that lymphoma develops in response to areas of localised autoimmune stimulation. Although this would make you think patients with Hashimoto's should develop the MALT lymphoma in thyroid tissue (which they frequently do), they also frequently develop gastric lesions, which do not respond to *Helicobacter pylori* triple-therapy.

There is no evidence to suggest that **smoking** is linked to the development of MALT lymphomas.

There is no evidence to suggest that **alcoholism** is linked to the development of MALT lymphomas.

Although **GORD** is a frequent symptom in patients with MALT lymphomas, it is not known to actually cause MALT lymphomas, and therefore, this is not the correct answer.

No evidence suggests **type-2 diabetes mellitus** is linked to the development of MALT lymphomas.

Discuss (1) Improve

Next question

Hashimoto's thyroiditis

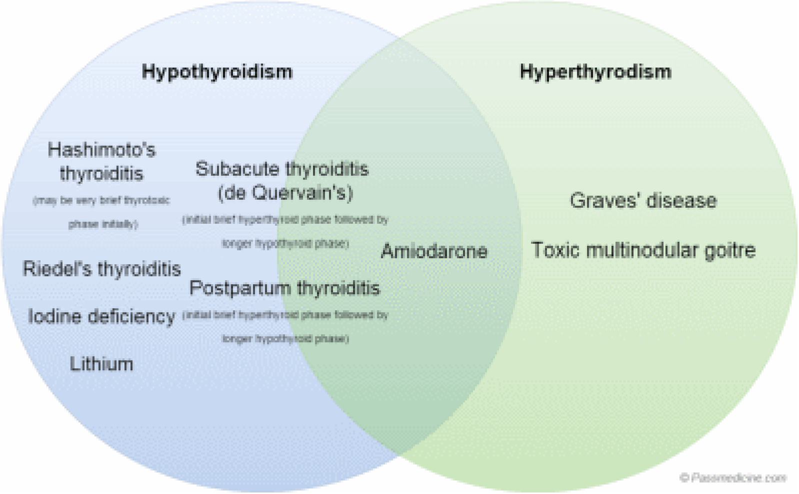
Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features

- features of hypothyroidism
- goitre: firm, non-tender
- anti-thyroid peroxidase (TPO) and also anti-thyroglobulin (Tg) antibodies

Associations

- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of MALT lymphoma


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Graves' disease
Toxic multinodular goitre
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

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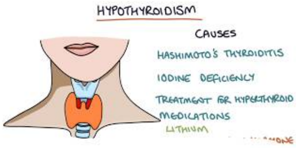
HYPOTHYROIDISM
CAUSES
HASHIMOTO'S THYROIDITIS
IODINE DEFICIENCY
TREATMENT FOR HYPERTHYROID
MEDICATIONS
LITHIUM

Hypothyroidism and Hashimoto's Thyroiditis: Visual Explanation for Students

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Score: **23.2%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓

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Question 229 of 414 ×

A 22-year-old man presents to the emergency department with left-sided loin pain, suspecting a renal stone. He has a past medical history of recurrent renal stones, dry eyes and dry mouth currently under investigation.

On examination, he has left-sided flank tenderness. Observations are within normal limits except for a heart rate of 102 bpm. A venous blood gas is performed, as well as an X-ray:

pH	7.32	(7.35 - 7.45)
$PaCO_2$	5.2 kPa	(4.7 - 6.0)
HCO_3^-	15 mEq/L	(22 - 26)
Na^+	140 mmol/L	(135 - 145)
K^+	3.1 mmol/L	(3.5 - 5.0)
Chloride	117 mEq/L	(96 - 106)
Abdominal X-ray	Calcification within the urinary tract	

What is the most likely diagnosis?

🟩	Renal tubular acidosis type 1	68%
🟥	Renal tubular acidosis type 2	20%
	Renal tubular acidosis type 3	5%
	Renal tubular acidosis type 4	7%
	Renal tubular acidosis type 5	1%

Distal renal tubular acidosis can cause calcium phosphate renal stones and is linked to Sjogrens syndrome

Important for me Less important

This patient's presentation is suggestive of a recurrence of renal stones. His past history suggests an underlying diagnosis of renal tubular acidosis (RTA), a clinical syndrome characterised by hyperchloraemic metabolic acidosis with a normal anion gap as seen here. Specifically, this patient is likely to have **RTA type 1**, also known as classic distal RTA. This is commonly linked to hypokalaemia, recurrent renal stones and nephrocalcinosis. It is strongly linked to numerous causes, including rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome; the latter is hinted at in this scenario by the history of dry mouth and dry eyes.

RTA type 2 (proximal RTA) is incorrect. While this is also linked to hypokalaemia, its causes typically include Wilson's disease, cystinosis and certain medications. It is linked with Fanconi syndrome. The association with probable Sjogren's syndrome here suggests RTA type 1 instead.

RTA type 3 (mixed RTA) is extremely rare and caused by carbonic anhydrase II deficiency. RTA type 1 is more common and, given the link with probable Sjogren's syndrome here, the more likely option.

RTA type 4 is incorrect. This presents with hyperkalaemia, rather than hypokalaemia. Causes include diabetes mellitus and hypoaldosteronism.

RTA type 5 is incorrect. This is not a recognised subtype of RTA.

👍 👎 💬 Discuss (2) Improve

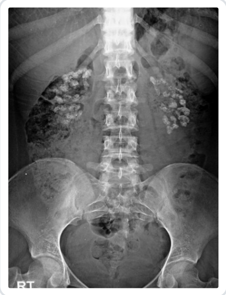
Next question

Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

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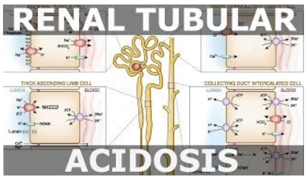

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Question 230 of 414 ✓

A 58-year-old gentleman with longstanding type 2 diabetes presents to the acute medical take. Blood tests are demonstrated in the table below. The blood test results are consistent with diabetic ketoacidosis. He has no other past medical history other than type 2 diabetes and obesity. He has not had episodes of diabetic ketoacidosis before and does not drink alcohol. His medication history includes aspirin, losartan, metformin, dapagliflozin and glimepiride. He is allergic to penicillin.

pH	7.26
Blood ketones	3.6 mmol/L
Blood sugar	15 mmol/L

Which of his medications is most likely to have contributed to developing diabetic ketoacidosis?

Metformin	16%
Dapagliflozin	63%
Glimepiride	11%
Aspirin	4%
Losartan	5%

Dapagliflozin is a newer drug for the treatment of diabetes. It is a member of the sodium-glucose transport protein 2 (SGLT2) inhibitor class of drugs.

SGLT2 inhibitors prevent the resorption of glucose from the proximal renal tubule, resulting in more glucose being secreted in the urine.

The other medications in this class include: canagliflozin & empagliflozin

Importantly, whilst these medications represent an effective class of drugs, there are reports of patients with type 2 diabetes presenting in diabetic ketoacidosis whilst taking them. It essential that acute medical teams are vigilant for such presentations as the prevalence of SGLT2 inhibitor prescribing increases.

The other possible answers (metformin / glimepiride / aspirin / losartan) are not associated with the development of diabetic ketoacidosis. It should, of course, be noted that metformin can lead to a lactic acidosis.

Source: UK Government Drug Safety Bulletin (https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis)

👍 👎 Discuss (4) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

Textbooks

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Links

BNF 👍 3 👎 9

Dapagliflozin

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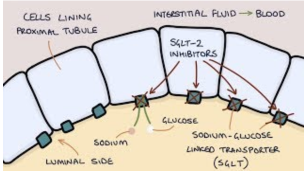
Media


CELLS LINING PROXIMAL TUBULE
INTERSTITIAL FLUID → BLOOD
SGLT-2 INHIBITORS
GLUCOSE
SODIUM
SODIUM-GLUCOSE LINKED TRANSPORTER (SGLT)
LUMINAL SIDE

How does Dapagliflozin work? Understanding SGLT2 inhibitors.

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Score: **23.5%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗

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Question 231 of 414 ✗

You are called to see a 34 year-old man in the late afternoon while you are on-call. He suffers with type 1 diabetes mellitus and was admitted after being diagnosed with diabetic ketoacidosis. He has been treated with a fixed-rate insulin infusion with potassium replacement. He usually takes Lantus glargine and Novorapid insulins, but the nurses have not been administering these while he has been on his insulin infusion. His latest arterial blood gas is shown:

pH	7.37
pCO2	4.3 kPa
pO2	11.9 kPa
BIcarbonate	26 mmol/L
Glucose	5.2 mmol/L

What is the best course of action?

	Stop insulin infusion now and restart normal insulin regimen	25%
	Give Novorapid insulin, then stop insulin infusion with next meal	14%
🟥	Continue insulin infusion overnight	6%
	Give 10g oral glucose	5%
🟩	Give Lantus glargine, then stop insulin infusion with next meal	50%

Stopping an insulin infusion in the context of an insulin-dependent diabetic needs to be done with care. Long-acting insulins should be continued throughout the duration of any insulin infusion, but in this case this has not occurred - a not-uncommon problem on the wards.

The key focus here is that an insulin-dependent diabetic should never be without insulin as they risk precipitating diabetic ketoacidosis (DKA). Option A will leave a gap in insulin therapy (the patient's next insulin dose will be novorapid due with dinner) and risk recurrence of DKA. Option B gives only a short acting insulin, which will have worn off by the time the patient has his next meal. Option C is a safe choice, but this patient no longer requires an insulin infusion as evidenced by his normalised pH and blood glucose and continuing the infusion (with the attendant hourly blood glucose checking) overnight is not in the patient's best interests. Option D is inappropriate as the patient's blood glucose is in the normal range. Option E is therefore the correct option - it allows the patient's long-acting insulin to take effect before stopping the insulin infusion. He should also restart his Novorapid insulin with his next meal.

👍 👎 Discuss (8) Improve

Next question

Diabetic ketoacidosis ★

Diabetic ketoacidosis (DKA) may be a complication of existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

Pathophysiology

- DKA is caused by uncontrolled lipolysis (not proteolysis) which results in an excess of free fatty acids that are ultimately converted to ketone bodies

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction.

Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

Diagnostic criteria

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
Key points • glucose > 13.8 mmol/l • pH < 7.30 • serum bicarbonate <18 mmol/l	Key points • glucose > 11 mmol/l or known diabetes mellitus • pH < 7.3 • bicarbonate < 15 mmol/l

American Diabetes Association (2009)	**Joint British Diabetes Societies (2013)**
• anion gap > 10 • ketonaemia	• ketones > 3 mmol/l or urine ketones ++ on dipstick

Management

Main principles of management

- fluid replacement
  - most patients with DKA are deplete around 5-8 litres
  - isotonic saline is used initially, even if the patient is severely acidotic
  - please see an example fluid regime below.
- insulin
  - an intravenous infusion should be started at 0.1 unit/kg/hour
  - once blood glucose is < 14 mmol/l an infusion of 10% dextrose should be started at 125 mls/hr *in addition* to the 0.9% sodium chloride regime
- correction of electrolyte disturbance
  - serum potassium is often high on admission despite total body potassium being low
  - this often falls quickly following treatment with insulin resulting in hypokalaemia
  - potassium may therefore need to be added to the replacement fluids
  - if the rate of potassium infusion is greater than 20 mmol/hour then cardiac monitoring may be required
- long-acting insulin should be continued, short-acting insulin should be stopped

JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over

Fluid	Volume
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	**Potassium replacement in mmol/L of infusion solution**
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Resolution

DKA resolution is defined as:

- pH >7.3 and
- blood ketones < 0.6 mmol/L and
- bicarbonate > 15.0mmol/L

Further points

- both the ketonaemia and acidosis should have been resolved within 24 hours. If this hasn't happened the patient requires senior review from an endocrinologist
- if the above criteria are met and the patient is eating and drinking switch to subcutaneous insulin
- the patient should be reviewed by the diabetes specialist nurse prior to discharge

Complications

Complications may occur from DKA itself or the treatment:

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia
- acute respiratory distress syndrome
- acute kidney injury

* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

Next question

Textbooks

High-yield textbook

Extended textbook

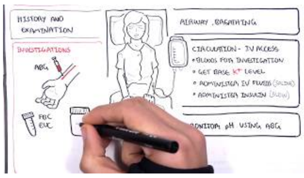
Links

Joint British Inpatient Diabetes Societies Inpatient Care Group 👍 8 👎 4

The Management of Diabetic ketoacidosis in adults

Report broken link

Media


HISTORY AND EXAMINATION
INVESTIGATIONS
ABG
FBC
EUC
AIRWAY, BREATHING
CIRCULATION - IV ACCESS
• BLOODS FOR INVESTIGATION
• GET BASE K+ LEVEL
• ADMINISTER IV FLUIDS (SALINE)
• ADMINISTER INSULIN (SLOW)
MONITOR pH USING ABG

Diabetic Ketoacidosis (Diabetes Type I) Management Summary

Armando Hasudungan - YouTube 👍 14 👎 1

PassMedicine

Question 232 of 414 ✗

A 20-year-old patient presents with persistent polyuria, polydipsia and fatigue. Blood and urine dip tests demonstrate hyperglycaemia but are consistently negative for ketones. The patient's father has a similar problem. The patient is started on gliclazide and responds well to this treatment.

What is the typical inheritance pattern of the likely underlying diagnosis?

🟩	Autosomal dominant	79%
	Autosomal recessive	8%
	Not an inherited disorder	7%
🟥	X-linked dominant	3%
	X-linked recessive	2%

MODY is inherited in an autosomal dominant fashion so a family history is often present

Important for me Less important

This patient presents with typical features of maturity-onset diabetes of the young (MODY). This condition normally presents in patients under the age of 25 with a family history of early-onset diabetes. The lack of ketosis and good response to a sulfonylurea is also consistent with a diagnosis of MODY. MODY is inherited in an autosomal dominant fashion.

An example of a condition that is inherited in an autosomal recessive fashion is cystic fibrosis. MODY is inherited in an autosomal dominant, rather than recessive, fashion.

MODY is normally an inherited condition, therefore 'not an inherited disorder' is an incorrect answer.

An example of a condition that is inherited in an X-linked dominant fashion is fragile X syndrome.

An example of a condition that is inherited in an X-linked recessive fashion is red-green colour blindness.

Discuss (4) | Improve

Next question

MODY ★

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **23.3%**

1 ✓

PassMedicine

Question 233 of 414 ✕

A 42-year-old woman presents with progressively worsening weight loss, anxiety, heat intolerance, and dry skin and eyes.

Hyperthyroidism is confirmed on thyroid-function tests and the patient is commenced on carbimazole. A set dose is initially started with a plan to titrate up the drug until the patient becomes euthyroid. Further thyroid hormone testing is scheduled in 4 to 6 weeks.

What is the mechanism of action of this medication?

	Blocks thyroxine-binding globulin	12%
	Enhances thyroid peroxidase	3%
	Inhibiting 5'-deiodinase	9%
🟩	Prevents iodination of the tyrosine residue on thyroglobulin	61%
🟥	Prevents thyroxine (T4) conversion to triiodothyronine (T3)	15%

Carbimazole blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production

Important for me Less important

This patient has presented with clinical features and investigations in keeping with a diagnosis of thyrotoxicosis/hyperthyroidism and has therefore been started on the common first line-treatment carbimazole. This medication blocks thyroid peroxidase thereby **preventing the iodination of the tyrosine residue on thyroglobulin**. This results in a reduction in excessive thyroid hormone production that results in the signs and symptoms of thyrotoxicosis.

Thyroxine-binding globulin (TBG) is one of three transport proteins (the others being transthyretin and serum albumin) responsible for carrying the thyroid hormones T4 & T3 in the body's circulation. TBG is unaffected by carbimazole and, in theory, any drug that **blocked thyroxine-binding globulin** would increase the amount of free T4 & T3 hormones, exacerbating the features of hyperthyroidism.

Antithyroid drugs such as carbimazole work by inhibiting, **not enhancing thyroid peroxidase**, resulting in a reduction of thyroid hormone production.

It is the antithyroid drug propylthiouracil that also **inhibits 5'-deiodinase** peripherally, preventing the conversion of T4 to T3. Carbimazole does not affect 5-deiodinase and only works via the central mechanism of blocking thyroid peroxidase.

Again it is the antithyroid drug propylthiouracil and not carbimazole which is responsible for **prevents thyroxine (T4) conversion to triiodothyronine (T3)** via the inhibiting of 5'-deiodinase.

Discuss (1) Improve

Next question

Carbimazole ★

Carbimazole is used in the management of thyrotoxicosis. It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.

Mechanism of action
- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production
- in contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5'-deiodinase which reduces peripheral conversion of T4 to T3

Adverse effects
- agranulocytosis
- crosses the placenta, but may be used in low doses during pregnancy

Next question

Textbooks

PassMedicine

← Question 234 of 414 ✗ ⚐ →

A 27-year-old female develops eye pain and reduced visual acuity following the initiation of treatment for her recently diagnosed Grave's disease. Which one of the following treatments is likely to have been started?

Radioiodine treatment	59%
Thyroidectomy	2%
Propylthiouracil	13%
Carbimazole and thyroxine	6%
Carbimazole	19%

Radioiodine treatment may lead to the development / worsening of thyroid eye disease in up to 15% of patients with Grave's disease

👍 👎 Discuss (1) Improve

Next question

Thyroid eye disease ★

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease

- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

Features
- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eyelids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

Management
- smoking cessation
- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

Complications

Exposure keratopathy
- this is the most common complication of thyroid eye disease
- due to eyelid retraction and proptosis (exophthalmos) → cornea becomes excessively exposed, disrupting the normal tear film → dryness, irritation, and corneal ulceration
- symptoms include foreign body sensation, pain, and photophobia
- in severe cases, it can lead to corneal scarring and vision impairment.

Optic neuropathy
- one of the most serious complications of thyroid eye disease
- occurs when enlarged extraocular muscles compress the optic nerve at the apex of the orbit → a reduction in visual acuity, colour vision deficits, and visual field defect
- it requires urgent medical intervention to prevent permanent vision loss.

Strabismus and diplopia
- fibrosis and enlargement of the extraocular muscles can result in restrictive strabismus → misalignment of the eyes → double vision (diplopia)
- this not only affects visual function but can also significantly impair the quality of life.

Monitoring patients with established thyroid eye disease

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Consensus Statement of the European Group on Graves' Orbitopathy 👍 2 👎 1

Management of Graves' Orbitopathy

Report broken link

Score: **23.1%**

1 ✓

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Question 235 of 414 ✗

You are reviewing the blood results for a patient who was started on atorvastatin 20mg on for primary prevention 3 months ago:

	Recent	**3 months ago prior to starting treatment**
Total cholesterol	4.2 mmol/l	6.3 mmol/l
HDL cholesterol	1.1 mmol/l	1.0 mmol/l
Non-HDL cholesterol	2.1 mmol/l	4.0 mmol/l
Triglyceride	1.2 mmol/l	1.3 mmol/l

Liver function tests are normal.

What is the most appropriate course of action?

	Reduce atorvastatin to 10mg on	7%
🟩	Make no changes to medication	72%
	Increase atorvastatin to 40mg on	12%
🟥	Check creatine kinase	5%
	Check compliance	5%

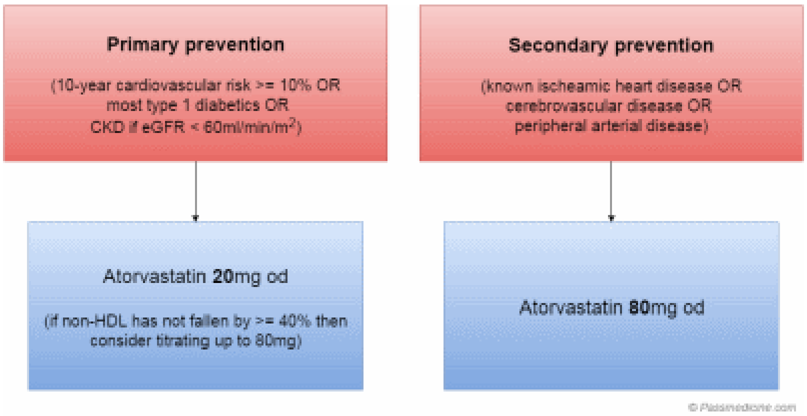
NICE look for a 40% reduction in non-HDL cholesterol after 3 months. A 10% reduction in a non-HDL cholesterol of 4.0 would be 0.4 so a 40% reduction would take it down to (4.0 - 1.6 = 2.4 mmol/l). This patients non-HDL cholesterol of 2.1 mmol/l is therefore acceptable.

Discuss (5) Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months
- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet
- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management
- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake
- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation
- smokers should be encouraged to quit

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 9 👎 6

2014 Lipid modification guidelines

Clinical Knowledge Summaries

PassMedicine

Question 236 of 414

A 32-year-old woman who is 18 weeks pregnant attends the antenatal clinic. She had an oral glucose tolerance test (OGTT) at her booking visit due to a family history of type II diabetes mellitus.

The results at the 12-week booking were:

Fasting glucose	6.1 mmol/L	Normal <5.6 mmol/L
2-hour post glucose challenge	9.2 mmol/L	Normal <7.8mmol/L

A decision is made to start metformin 500mg twice daily and she is provided with information leaflets regarding diet and lifestyle modification.

On review today at 18 weeks gestation her repeat OGTT results are as follows:

Fasting glucose	6.0 mmol/L	Normal <5.3 mmol/L
2-hour post glucose challenge	7.2 mmol/L	Normal <6.4 mmol/L

What is the next most appropriate action with regards to the management of her blood glucose?

Add insulin	66%
No change to treatment	7%
Refer for specialist dietary and exercise intervention	3%
Increase metformin to 1g twice daily	20%
Repeat results in two weeks time and consider intensification of treatment	4%

In gestational diabetes, if blood glucose targets are not met with diet/metformin then insulin should be added

Important for me Less important

The patient here has a diagnosis of gestational diabetes from the initial booking appointment. An initial trial of metformin has not been successful as the fasting and two-hour post glucose challenge blood glucose levels are elevated above the normal range. Where metformin has not been successful at controlling established gestational diabetes, insulin should be added. The correct answer therefore in this circumstance is insulin.

No change to treatment is the incorrect answer, as the patient here continues to have impaired glycaemic control. If no action is taken then there are increased risks to the foetus through the development of polyhydramnios or macrosomia.

Referral for dietary and exercise regimens may be considered alongside the current treatments, however, this is likely to be the first-line intervention. Where this has failed further escalation of medical therapy is required for the health of the foetus.

Increasing the dose of metformin in incorrect. The NICE guidelines state that where initial exercise, dietary and a trial of metformin have been unsuccessful then insulin should be started. Increasing the dose of metformin and waiting for a response may delay necessary control of the patient's blood glucose.

Repeating the results in two weeks will delay the necessary intensification of treatment. Treatment intensification to insulin is required at today's clinic appointment.

Discuss (7) | Improve

Next question

Gestational diabetes

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:
- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes
- BMI of $> 30\ kg/m^2$

- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
  - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
  - if glucose targets are still not met insulin should be added to diet/exercise/metformin
  - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts

- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

NICE 👍 3 👎 5

2015 Management of diabetes in pregnancy

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Question 237 of 414 ✗

A 54-year-old-woman with known ovarian cancer presents with confusion. She has become progressively confused over the last few days, and prior to that, she had started to become constipated. Her family describes poor oral intake of fluids and poor urinary output as well. On further discussion with the family, they mention that she was seen in oncology clinic two weeks ago with results of a bone scan which they had been told was normal.

On examination, she appears dehydrated.

Hb	147 g/l
Platelets	321 * 10^9/l
WBC	7.8 * 10^9/l
Na^+	142 mmol/l
K^+	4.7 mmol/l
Urea	4.6 mmol/l
Creatinine	92 µmol/l
Corrected calcium	3.2 mmol/l
Parathyroid hormone	Pending

What is the most likely cause of her elevated calcium?

	Osteolytic hypercalcaemia	9%
	Calcitriol-mediated hypercalcaemia	3%
🟥	Ectopic PTH secretion	25%
🟩	Parathyroid-hormone-related peptide release	49%
	Primary hyperparathyroidism	13%

The correct answer is parathyroid-hormone-related peptide release. Whilst this is classically described as secondary to squamous cell lung cancer, it can occur in many malignancies.The two most common causes of hypercalcaemia are malignancy and primary hyperparathyroidism. In malignancy, roughly 80% of cases are due to parathyroid-hormone-related peptide release. The vast majority of remaining cases are due to osteolysis, and some due to calcitriol-mediated hypercalcaemia and ectopic PTH secretion. Primary hyperparathyroidism is another common cause but is not as likely as malignant hypercalcaemia given the known diagnosis of ovarian cancer.

Source:

'Hypercalcaemia of Malignancy.' BMJ Best Practice. 14 June 2016.

👍 👎 Discuss (5) Improve

Next question

Hypercalcaemia: causes

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
  - PTHrP from the tumour e.g. squamous cell lung cancer
  - bone metastases
  - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include

- sarcoidosis
  - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:
  - thiazides
  - calcium-containing antacids
- dehydration

- Addison's disease
- Paget's disease of the bone
  - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

Textbooks

High-yield textbook

Extended textbook

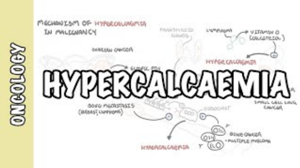
Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€“ presentation and management

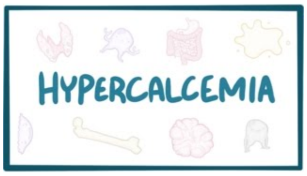
Report broken link

Media


ONCOLOGY
HYPERCALCAEMIA
MECHANISM OF HYPERCALCAEMIA IN MALIGNANCY

Hypercalcemia in malignancy

Armando Hasudungan - YouTube 👍 19 👎 2


HYPERCALCEMIA

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Question 238 of 414 ✓

An 80-year-old woman presents with increased urinary frequency, a recurrent feeling of needing to urinary and episodes of incontinence. The patient is generally frail but has no other symptoms and is not on any regular medications.

A trial of pelvic floor muscle exercises and bladder retraining has minimal improvement and therefore the patient is commenced on a bladder stabilising drug for urge incontinence.

A few days later the patient is admitted to the hospital with acute confusion attributed to an adverse effect of this new medication.

What drug was the patient most likely commenced on?

Darifenacin	2%
Duloxetine	15%
Mirabegron	20%
Oxybutynin	57%
Tolterodine	6%

Oxybutynin should not be used in frail older women with urinary incontinence due to the risk of impairment of daily functioning, confusion and acute delirium

Important for me Less important

This patient originally presented with urinary incontinence predominantly due to urge incontinence or an overactive bladder. If bladder retraining techniques are unsuccessful, bladder stabilisers in the form of antimuscarinics are recommended as first-line treatment. **Oxybutynin** is commonly used as an immediate release bladder stabiliser however it should be avoided in frail patients who are at risk of cognitive decline as it has been associated with reduced function, confusion and acute delirium. It is thought that oxybutynin has a higher propensity than other bladder stabilisers to increase dopamine concentration within the brain synaptic clefts resulting in these adverse side effects.

Duloxetine may be used in the management of urinary incontinences but in cases where stress incontinence is the predominant issue, not urge incontinence as in this case; duloxetine is not used as a bladder stabiliser. Duloxetine is a combined noradrenaline and serotonin reuptake inhibitor that is thought to increase stimulation of the urethral striated muscles within the sphincters and therefore reduces stress incontinence. Delirium and cognitive decline are very rare in serotonin and norepinephrine reuptake inhibitors and normally only result from additional drug interaction.

Darifenacin is a once-daily anticholinergic agent which can also be used as a bladder stabiliser. Unlikely oxybutynin, darifenacin has a much lower risk of cognitive decline or delirium and therefore patients may be switched if they experience these adverse effects. Like most anticholinergic agents darifenacin can still cause other side effects including constipation, blurred vision and urinary retention.

Mirabegron is a beta-3 agonist that can be used as an alternative bladder stabiliser to anticholinergic agents in urinary incontinence. As a beta-3 agonist, it is thought to relax the detrusor smooth muscle when storing urine, increase the bladder capacity and alleviate urgency and frequency symptoms. Mirabegron is often used in patients at risk of adverse effects from antimuscarinic agents.

Tolterodine is another immediate release anticholinergic agent used to manage urge incontinence but again it is not commonly associated with delirium or cognitive decline. In incidence where these adverse effects have occurred, concomitant drug interactions are normally identified as the cause.

Discuss (2) Improve

Next question

Urinary incontinence

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation
- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:
- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:
- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the

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Question 239 of 414 ✗

Which of the following secondary causes of hyperlipidaemia result in predominantly hypercholesterolaemia, as opposed to hypertriglyceridaemia?

Hypothyroidism	46%
Obesity	13%
Liver disease	17%
Bendrofluazide	11%
Chronic renal failure	14%

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

Important for me Less important

The correct answer is **Hypothyroidism**. Hypothyroidism can cause predominantly hypercholesterolaemia, as opposed to hypertriglyceridaemia. This is due to the fact that thyroid hormones play a crucial role in lipid metabolism. In hypothyroidism, there is a reduction in the liver's ability to take up and degrade low-density lipoprotein (LDL) cholesterol, leading to an increase in plasma LDL levels. Additionally, hypothyroidism reduces the activity of lipoprotein lipase, an enzyme that helps break down triglycerides, but this effect isn't as pronounced as the impact on LDL cholesterol.

Obesity does contribute to hyperlipidaemia, but it is more associated with hypertriglyceridaemia rather than hypercholesterolaemia. Obesity leads to increased free fatty acid flux to the liver which results in overproduction of very-low-density lipoprotein (VLDL), leading primarily to elevated triglyceride levels.

Liver disease, particularly cirrhosis and non-alcoholic fatty liver disease (NAFLD), can result in dyslipidaemia. However, this usually manifests as decreased levels of high-density lipoprotein (HDL) cholesterol and increased triglyceride levels rather than increased LDL cholesterol.

Bendrofluazide, a thiazide diuretic used for hypertension management, can indeed cause dyslipidaemia. However, its effect on lipid profile usually includes mild increases in both total cholesterol and triglycerides rather than a predominant rise in cholesterol alone.

Lastly, **Chronic renal failure** can lead to various lipid abnormalities known collectively as uremic dyslipidemia. This typically includes elevated triglycerides and reduced HDL cholesterol levels while effects on LDL cholesterol are variable.

👍 👎 Discuss (2) Improve

Next question

Hyperlipidaemia: secondary causes ★

Causes of predominantly hypertriglyceridaemia
- diabetes mellitus (types 1 and 2)
- obesity
- alcohol
- chronic renal failure
- drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- liver disease

Causes of predominantly hypercholesterolaemia
- nephrotic syndrome
- cholestasis
- hypothyroidism

Next question

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← Question 240 of 414 ✗ ⚐ →

A 33-year-old man with tingling in his thumb, index and middle finger has been referred for endocrine consultation. He also complains of waking up incredibly tired and says his wife complains that he snores. On examination, he is noted to have a prominent brow ridge. Looking at old photos, it becomes clear that his facial appearance has drastically changed over time. After some blood tests and an MRI scan, he is prescribed octreotide. What is the mechanism of action of this drug?

🟩	Somatostatin analogue	81%
	Growth hormone receptor antagonist	11%
	Dopamine agonist	2%
	Dopamine antagonist	2%
🟥	Insulin-growth factor 1 antagonist	5%

Acromegaly is caused by excessive growth hormone. Somatostatin directly inhibits the release of growth hormone, and hence somatostatin analogues are used to treat acromegaly

Important for me Less important

This question is two-fold. First, one has to recognise the symptoms of acromegaly. Carpal tunnel syndrome and sleep apnoea are classic complications of acromegaly. The changing nature of his face over time is another clue. The second part of the question was to acknowledge that octreotide, a useful treatment for acromegaly is a somatostatin analogue.

Dopamine agonists were initially used to treat acromegaly but have fallen out of favour due to superior treatments. Dopamine antagonists have never been a treatment for acromegaly. An example of a growth hormone antagonist is pegvisomant. Growth hormone stimulates insulin growth factor-1 release from the liver, but antagonists have not been developed yet.

👍 👎 Discuss Improve

Next question

Acromegaly: management ★

Trans-sphenoidal surgery is the first-line treatment for acromegaly in the majority of patients.

If a pituitary tumour is inoperable or surgery unsuccessful then medication may be indicated:

- somatostatin analogue
    - directly inhibits the release of growth hormone
    - for example octreotide
    - effective in 50-70% of patients
- pegvisomant
    - GH receptor antagonist - prevents dimerization of the GH receptor
    - once daily s/c administration
    - very effective - decreases IGF-1 levels in 90% of patients to normal
    - doesn't reduce tumour volume therefore surgery still needed if mass effect
- dopamine agonists
    - for example bromocriptine
    - the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
    - effective only in a minority of patients

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

Next question

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Question 241 of 414

A 62-year-old man is investigated for hypertension and proximal myopathy. On examination he is noted to have abdominal striae. Which one of the following is most associated with ectopic ACTH secretion?

Carcinoid tumour	5%
Small cell lung cancer	76%
Cardiac myxoma	1%
Squamous cell lung cancer	14%
Adrenal carcinoma	5%

Small cell lung cancer accounts 50-75% of case of ectopic ACTH

Important for me Less important

Adrenal carcinoma and cardiac myxoma are causes of ACTH independent Cushing's syndrome

Discuss (2) Improve

Next question

Cushing's syndrome: causes

It should be noted that exogenous causes of Cushing's syndrome (e.g. glucocorticoid therapy) are far more common than endogenous ones.

ACTH dependent causes
- Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
- ectopic ACTH production (5-10%): e.g. small cell lung cancer is the most common causes

ACTH independent causes
- iatrogenic: steroids

- iatrogenic: steroids
- adrenal adenoma (5-10%)
- adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma
- micronodular adrenal dysplasia (very rare)

Pseudo-Cushing's

- mimics Cushing's
- often due to alcohol excess or severe depression
- causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- insulin stress test may be used to differentiate

Next question

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Side-effects of systemic steroids

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CUSHING SYNDROME

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Question 242 of 414 ✓

Which one of the following conditions may cause hypokalaemia in association with hypertension?

Gitelman syndrome	13%
21-hydroxylase deficiency	17%
Bartter's syndrome	16%
Phaeochromocytoma	19%
11-beta hydroxylase deficiency	36%

11-beta hydroxylase deficiency associated with hypertension

Important for me Less important

21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

Discuss (12) Improve

Next question

Hypokalaemia and hypertension

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not

Hypokalaemia with hypertension
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
- 11-beta hydroxylase deficiency*

Carbenoxolone, an anti-ulcer drug, and liquorice excess can potentially cause hypokalaemia associated with hypertension

Hypokalaemia without hypertension

- diuretics
- GI loss (e.g. Diarrhoea, vomiting)
- renal tubular acidosis (type 1 and 2**)
- Bartter's syndrome
- Gitelman syndrome

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**type 4 renal tubular acidosis is associated with hyperkalaemia

Next question

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Hypokalemia - causes, symptoms, diagnosis, treatment, pathology

Osmosis - YouTube 👍 14 👎 3

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Question 243 of 414

Which of the following is most likely to cause hypokalaemia associated with acidosis?

Cushing's syndrome	11%
Vomiting	16%
Conn's syndrome	20%
Diuretics	12%
Acetazolamide	41%

Acetazolamide causes hypokalaemia

Important for me Less important

The correct answer is **Acetazolamide**. Acetazolamide is a carbonic anhydrase inhibitor that is used to treat conditions such as glaucoma, altitude sickness and certain types of oedema. It works by reducing the reabsorption of bicarbonate in the proximal tubule of the kidney, leading to metabolic acidosis. The body compensates for this acidosis by increasing potassium excretion in an attempt to retain more hydrogen ions, which can result in hypokalaemia.

Cushing's syndrome typically leads to hypokalaemia. However, this condition is characterised by excess cortisol production which promotes sodium retention and increases potassium excretion, but not to the extent that would cause the hypokalaemia associated with acidosis.

Vomiting can indeed lead to hypokalaemia due to loss of gastric fluids rich in potassium. However, it causes metabolic alkalosis rather than acidosis because loss of stomach acid (hydrochloric acid) reduces hydrogen ion concentration, causing the blood pH to increase.

Conn's syndrome, also known as primary hyperaldosteronism, can cause hypokalaemia due to increased aldosterone leading to enhanced potassium secretion in the distal tubules and collecting ducts of nephrons. However, Conn's Syndrome results in metabolic alkalosis rather than acidosis due to increased reabsorption of sodium and bicarbonate.

Finally, **Diuretics** can cause both hypokalaemia and metabolic alkalosis. Loop diuretics and thiazides increase sodium delivery to distal tubules causing increased exchange for potassium and hydrogen ions leading to their increased urinary excretion. But like vomiting and Conn's Syndrome, they are associated with alkalosis rather than acidosis because they promote bicarbonate reabsorption in the kidney.

Discuss (8) Improve

Next question

Hypokalaemia ★

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalaemia with alkalosis
- vomiting
- thiazide and loop diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis
- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

Next question

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← Question 244 of 414 ✗ ⚐ →

A 23-year-old woman presents for review. She has not had a normal period for around 8 months now. A recent pregnancy test was negative. Blood tests are ordered:

FSH	2.2 IU/L (0-20 IU/L)
Oestradiol	84 pmol/l (100-500 pmol/l)
Thyroid stimulating hormone	3.1 mIU/L
Prolactin	2 ng/ml (0-10 ng/ml)
Free androgen index	3 (< 7)

What is the most likely cause of her symptoms?

🟥 Prolactinoma	3%
Premature ovarian failure	42%
Polycystic ovarian syndrome	16%
Addison's disease	3%
🟩 Excessive exercise	36%

In a very athletic woman, hypothalamic hypogonadism is a common cause of secondary amenorrhoea

Important for me Less important

The bloods show a hypothalamic amenorrhoea which may be caused by stress or excessive exercise. The FSH would be raised in premature ovarian failure.

👍 👎 Discuss (11) Improve

Next question

Amenorrhoea ★

Amenorrhoea may be divided into:

- primary: defined as the failure to establish menstruation by 15 years of age in girls with normal secondary sexual characteristics (such as breast development), or by 13 years of age in girls with no secondary sexual characteristics
- secondary: cessation of menstruation for 3-6 months in women with previously normal and regular menses, or 6-12 months in women with previous oligomenorrhoea

Causes

Primary amenorrhoea	**Secondary amenorrhoea (after excluding pregnancy)**
• gonadal dysgenesis (e.g. Turner's syndrome) - the most common causes • testicular feminisation • congenital malformations of the genital tract • functional hypothalamic amenorrhoea (e.g. secondary to anorexia) • congenital adrenal hyperplasia • imperforate hymen	• hypothalamic amenorrhoea (e.g. secondary stress, excessive exercise) • polycystic ovarian syndrome (PCOS) • hyperprolactinaemia • premature ovarian failure • thyrotoxicosis* • Sheehan's syndrome • Asherman's syndrome (intrauterine adhesions)

Investigation and management

Initial investigations

- exclude pregnancy with urinary or serum bHCG
- full blood count, urea & electrolytes, coeliac screen, thyroid function tests
- gonadotrophins
  - low levels indicate a hypothalamic cause where as raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
  - raised if gonadal dysgenesis (e.g. Turner's syndrome)
- prolactin
- androgen levels
  - raised levels may be seen in PCOS
- oestradiol

Management

- primary amenorrhoea:
    - investigate and treat any underlying cause
    - with primary ovarian insufficiency due to gonadal dysgenesis (e.g. Turner's syndrome) are likely to benefit from hormone replacement therapy (e.g. to prevent osteoporosis etC)
- secondary amenorrhoea
    - exclude pregnancy, lactation, and menopause (in women 40 years of age or older)
    - treat the underlying cause

*hypothyroidism may also cause amenorrhoea

Next question

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Amenorrhoea

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AMENORRHEA
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Question 245 of 414 ✓

Which of the following statements is true regarding hyponatraemia?

In a dehydrated patient with urinary sodium < 20mmol/L it may be due to the diuretic stage of renal failure	17%
SIADH typically leads to urine osmolality of < 500 mmol/kg	12%
Hyperlipidaemia may cause pseudohyponatraemia	57%
Cardiac failure and liver cirrhosis may lead to primary hyperaldosteronism	7%
It is known to cause a long QT interval	7%

The correct answer is '**Hyperlipidaemia may cause pseudohyponatraemia**'. Pseudohyponatraemia refers to a laboratory artefact where the measured serum sodium concentration is lower than the actual physiologic concentration. This can occur in conditions with high plasma protein or lipid content, such as hyperlipidaemia, because these substances displace water and hence sodium in the plasma, leading to a falsely low sodium reading.

Discussing the incorrect options:

'**In a dehydrated patient with urinary sodium < 20mmol/L it may be due to the diuretic stage of renal failure**' is incorrect. In renal failure, especially during its diuretic phase, urinary sodium levels are typically elevated rather than decreased due to impaired tubular reabsorption of sodium.

'**SIADH typically leads to urine osmolality of < 500 mmol/kg**' is not accurate. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterised by an inability to dilute urine due to excessive release of ADH from the posterior pituitary gland. This results in concentrated urine with osmolality usually > 100 mOsm/kg higher than serum osmolality and often > 500 mOsm/kg.

'**Cardiac failure and liver cirrhosis may lead to primary hyperaldosteronism**' is not true. While these conditions can result in secondary hyperaldosteronism due to increased renin production as part of body's response to decreased blood flow through kidneys, they do not cause primary hyperaldosteronism which occurs due to autonomous overproduction of aldosterone usually from an adrenal adenoma or bilateral adrenal hyperplasia.

Finally, '**It is known to cause a long QT interval**' is incorrect. Hyponatraemia does not directly cause prolongation of the QT interval on electrocardiogram (ECG). It's worth noting that severe hyponatraemia can potentially lead to seizures and other neurological symptoms but these are not related to QT interval changes.

👍 👎 Discuss (2) Improve

Next question

Hyponatraemia ★

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis

Urinary sodium > 20 mmol/l

Sodium depletion, renal loss (patient often hypovolaemic)
- diuretics: thiazides, loop diuretics
- Addison's disease
- diuretic stage of renal failure

Patient often euvolaemic
- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

Urinary sodium < 20 mmol/l

Sodium depletion, extra-renal loss
- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)
- secondary hyperaldosteronism: heart failure, liver cirrhosis
- nephrotic syndrome
- IV dextrose

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Question 246 of 414 ✗

A 52-year-old man has a set of fasting bloods as part of a work-up for hypertension. The fasting glucose comes back as 6.5 mmol/l. The test is repeated and reported as 6.7 mmol/l. He says he feels constantly tired but denies any polyuria or polydipsia. How should these results be interpreted?

🟩	Impaired fasting glycaemia	66%
	Suggestive of diabetes mellitus but not diagnostic	5%
	Diabetes mellitus	10%
🟥	Normal	9%
	Impaired glucose tolerance	11%

The correct answer is **Impaired fasting glycaemia**. Impaired fasting glycaemia (IFG) is defined as a fasting plasma glucose level between 6.1 mmol/l and 6.9 mmol/l, according to the World Health Organization (WHO) criteria. In this case, the patient has two separate fasting glucose measurements of 6.5 mmol/l and 6.7 mmol/l, which fall within the IFG range. IFG is considered a pre-diabetic state and indicates an increased risk of developing type 2 diabetes mellitus in the future.

The option **Suggestive of diabetes mellitus but not diagnostic** is incorrect because a diagnosis of diabetes mellitus requires either a fasting plasma glucose level ≥7.0 mmol/l or an HbA1c ≥48 mmol/mol (6.5%) according to UK guidelines. In this case, the patient's fasting glucose levels are below the diagnostic threshold for diabetes mellitus.

The option **Diabetes mellitus** is also incorrect for the same reason mentioned above; the patient's fasting glucose levels do not meet the diagnostic criteria for diabetes mellitus.

The option **Normal** is incorrect because normal fasting plasma glucose levels are typically between 3.9 and 6.0 mmol/l in adults without diabetes, according to WHO guidelines. The patient's results are higher than this range, indicating impaired fasting glycaemia.

Finally, the option **Impaired glucose tolerance** is incorrect because impaired glucose tolerance (IGT) refers to a condition where blood sugar levels are elevated during an oral glucose tolerance test (OGTT), but not high enough to diagnose diabetes mellitus. IGT is diagnosed when 2-hour plasma glucose levels during an OGTT are between 7.8 and 11.mmol/l. In this case, the question does not mention an OGTT being performed, and the patient's fasting glucose levels do not fall within the IGT range.

👍 👎 Discuss (6) Improve

Next question

Diabetes mellitus (type 2): diagnosis ★

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic: **CKS**

- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

When HbA1c is used for the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis: **CKS**

- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

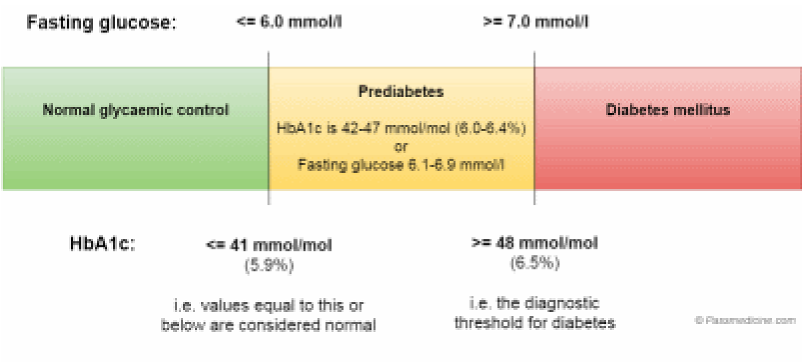
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or
below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic
threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

Impaired fasting glucose and impaired glucose tolerance

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:

- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Next question

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Clinical Knowledge Summaries 👍 2 👎 1

Type 2 diabetes mellitus: diagnosis

NICE 👍 2 👎 2

2022 Type 2 diabetes guidelines

Diabetes UK 👍 3 👎 4

New diagnostic criteria for diabetes

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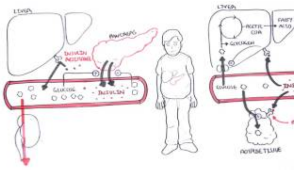
Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 8 👎 1

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Score: **23.2%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

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Question 247 of 414 ✓

A 54-year-old man with type 2 diabetes mellitus is reviewed in clinic. He is currently taking pioglitazone, metformin, aspirin and simvastatin. Which one of the following problems is most likely to be caused by pioglitazone?

Photosensitivity	7%
Thrombocytopaenia	6%
Myalgia	6%
Peripheral oedema	71%
Hyponatraemia	10%

Pioglitazone may cause fluid retention

Important for me Less important

The correct answer is **Peripheral oedema**. Pioglitazone, a type of thiazolidinedione, can cause fluid retention leading to peripheral oedema. This is due to its mechanism of action where it reduces insulin resistance and thus increases glucose uptake by the adipose tissue and skeletal muscle. This leads to an increase in plasma volume, which may result in peripheral oedema. It's particularly common in patients with underlying heart failure or those using insulin concurrently.

Discussing the other options:

Photosensitivity is not typically associated with pioglitazone. Photosensitivity reactions are more commonly seen with drugs such as tetracyclines, sulphonamides, thiazide diuretics, and some non-steroidal anti-inflammatory drugs (NSAIDs).

Thrombocytopaenia, a condition characterised by abnormally low levels of platelets in the blood, is also not a known side effect of pioglitazone. Drugs that are more commonly associated with thrombocytopenia include heparin, quinine, sulphonamides and some anticonvulsants.

Myalgia, or muscle pain, is not typically caused by pioglitazone either. Myalgia is more often associated with statins like simvastatin which this patient is also taking.

Lastly, **Hyponatraemia**, defined as a low sodium level in the blood, is not commonly caused by pioglitazone. Hyponatraemia can be induced by many classes of medications including diuretics, antidepressants (Selective serotonin reuptake inhibitors), antipsychotics and antiepileptics.

Discuss (4) Improve

Next question

Thiazolidinediones

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. It's natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

Next question

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← Question 248 of 414 ✗ ⚑ →

A 45-year-old man attends the GP for a health check. His cholesterol is found to be raised. He has a strong family history of high cholesterol. Genetic testing shows he is heterozygous for the affected allele.

If this man has a child with a woman who is not a carrier of the affected allele, what is the likelihood that the child will have the condition?

	0%	10%
	25%	24%
🟩	50%	64%
🟥	75%	1%
	100%	2%

Familial hypercholesterolaemia is an autosomal dominant condition

Important for me Less important

This question is testing your knowledge about inheritance. You should recall that familial hypercholesterolaemia is an autosomal dominant condition. A child born to this couple if 50% likely to have the condition. Drawing the genotypes of each parent is often helpful. This is often done using a Punnett square.

0% - this is not the correct answer. There will always be a chance of an affected child in an autosomal dominant condition. Drawing a Punnett square will show this.

25% - this is not the correct answer. Drawing a Punnett square can be helpful in this situation and will show that the likelihood of having an affected child is actually 50%.

50% - this is the correct answer. There is a 50% chance this child will be affected by the condition.

75% - this is not the correct answer. Drawing a Punnett square can be helpful in this situation and will show that the likelihood of having an affected child is actually 50%.

100% - this is not the correct answer. There will only be a 100% chance of a child having an autosomal condition if both partners are homozygous for the affected alleles.

👍 👎 Discuss (4) Improve

Next question

Familial hypercholesterolaemia ★

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Case finding:
- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
  - a total cholesterol level greater than 7.5 mmol/l and/or
  - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:
  - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
  - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome criteria**:
- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management
- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line

- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Next question

Textbooks

High-yield textbook

Extended textbook

Links

The FH Foundation 👍 3 👎 1

Simon Broom Criteria

The FH Foundation 👍 3 👎 1

High cholesterol during preganancy

NICE 👍 3 👎 1

2008 Familial hypercholesterolaemia guidelines

Public Library of Science (PLoS) 👍 2 👎 1

Cascade Screening for Familial Hypercholesterolemia (FH)

Report broken link

PassMedicine

← Question 249 of 414 ✗ ⚑ →

A 65-year-old man with a history of type 2 diabetes, ischaemic heart disease, and hypertension is reviewed in the clinic. His current antidiabetic medications include metformin, empagliflozin, and gliclazide. He has a BMI of 36 kg/mÂ², and his latest HbA1c level was 60 mmol/mol, measured one month ago.

What is the most appropriate next course of action?

	Add exenatide	19%
	Stop empagliflozin and start exenatide	5%
🟥	Stop empagliflozin and start insulin	2%
🟩	Stop gliclazide and start exenatide	65%
	Stop gliclazide and start insulin	9%

TD2M: if a triple combination of drugs has failed to reduce HbA1c then switching one of the drugs for a GLP-1 mimetic is recommended, particularly if the BMI > 35

Important for me Less important

The patient presents with poorly controlled diabetes, as evidenced by a recent HbA1c level exceeding 58 mmol/mol. He is also obese and currently takes three oral antidiabetic agents. The most suitable course of action would be to discontinue one of these medications and initiate treatment with a glucagon-like peptide-1 (GLP-1) mimetic, such as **exenatide**. Consistent with NICE guidelines, metformin should be maintained. Considering the patient's history of cardiovascular disease, it is advisable to continue his sodium-glucose cotransporter-2 (SGLT-2) inhibitor. Gliclazide may contribute to weight gain and thus represents the preferable option to cease in this obese individual.

Choosing **add exenatide** would not align with NICE recommendations, which advise discontinuation of one antidiabetic medication when a patient is on three agents before commencing a GLP-1 mimetic.

The choice to **stop empagliflozin and start exenatide** would not be favourable due to the patient's cardiovascular history. SGLT-2 inhibitors like empagliflozin have demonstrated mortality benefits in patients with cardiovascular disease; therefore, its continuation is warranted in this case.

Similarly, deciding to **stop empagliflozin and start insulin** would be less than ideal given the patient's cardiovascular profile. While initiating insulin therapy remains an alternative at this point, the patient's obesity means that a GLP-1 mimetic might be more fitting.

Lastly, the option to **stop gliclazide and start insulin** could be considered. Should insulin therapy commence, discontinuing gliclazide would reduce the risk of hypoglycaemic events. Nonetheless, due to the patient's obesity status, introducing a GLP-1 mimetic is deemed more suitable.

👍 👎 Discuss (1) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

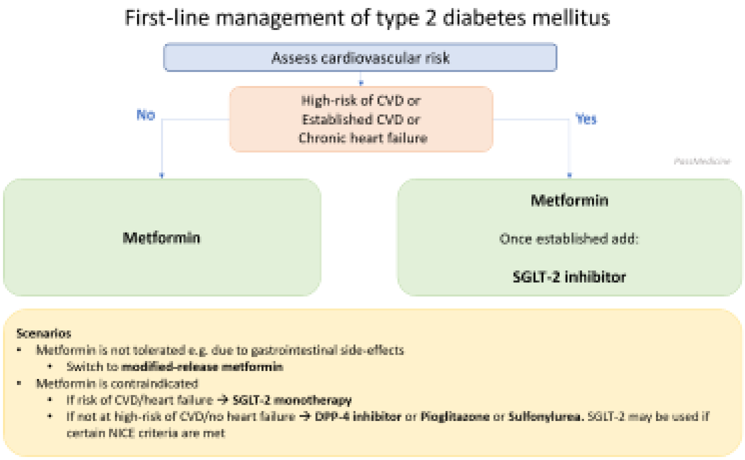
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or
Established CVD or
Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios
- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

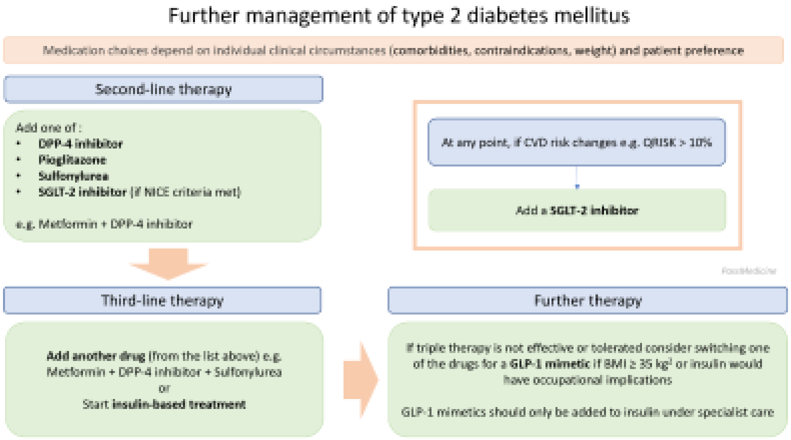
Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.
- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated
- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care
PassMedicine

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

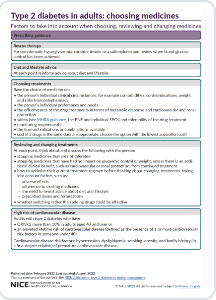
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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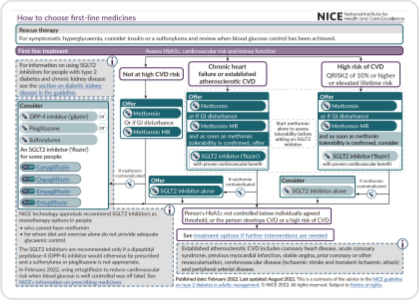

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider:
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR
If metformin contraindicated

Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit
If metformin contraindicated
Offer
SGLT2 inhibitor alone

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit
If metformin contraindicated
Consider
SGLT2 inhibitor alone

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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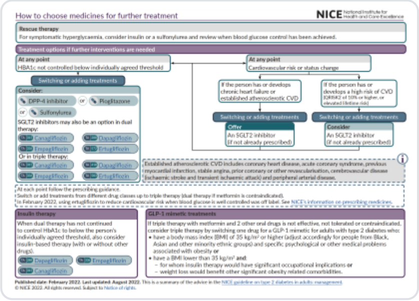

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold
Switching or adding treatments
Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Or in triple therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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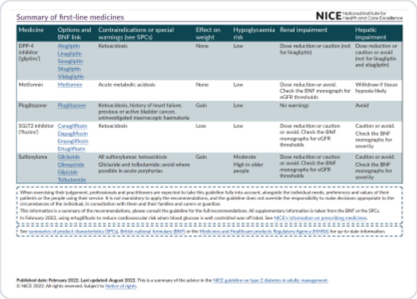

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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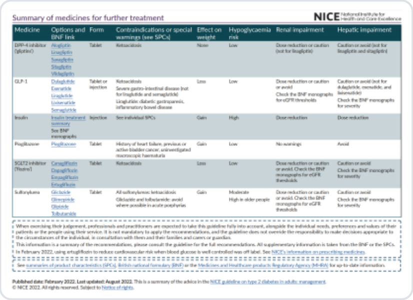

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

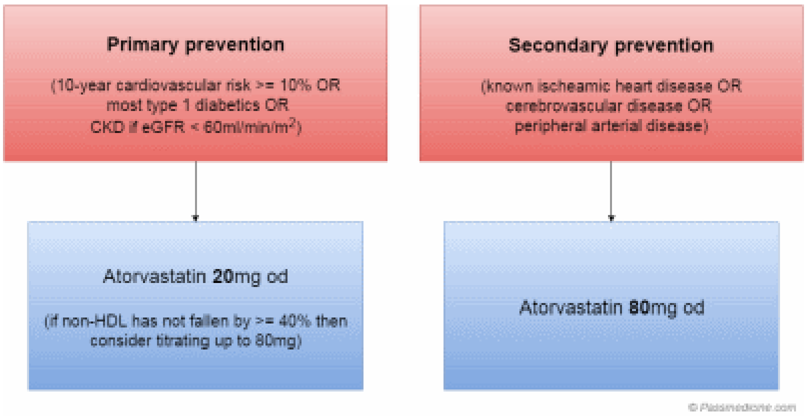
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

PassMedicine

← Question 250 of 414 ✗ →

Which one of the following is a recognised cause of hypokalaemia associated with hypertension

🟩	Liddle's syndrome	66%
	Bartter's syndrome	13%
	Gitelman syndrome	9%
🟥	Ciclosporin	2%
	Renal tubular acidosis	10%

Liddle's syndrome: hypokalaemia + hypertension

Important for me Less important

Liddle's syndrome is an autosomal dominant disorder that mimics hyperaldosteronism, resulting in hypokalaemia associated with hypertension.

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na^+ K^+ 2Cl- cotransporter in the ascending loop of Henle. It should be noted that it is associated with normotension.

Gitelman's syndrome is due to a defect in the thiazide-sensitive Na^+ Cl- transporter in the distal convoluted tubule. It is associated with hypokalaemia and normotension.

Discuss (8) Improve

Next question

Hypokalaemia and hypertension

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not

Hypokalaemia with hypertension

- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
- 11-beta hydroxylase deficiency*

Carbenoxolone, an anti-ulcer drug, and liquorice excess can potentially cause hypokalaemia associated with hypertension

Hypokalaemia without hypertension

- diuretics
- GI loss (e.g. Diarrhoea, vomiting)
- renal tubular acidosis (type 1 and 2**)
- Bartter's syndrome
- Gitelman syndrome

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**type 4 renal tubular acidosis is associated with hyperkalaemia

Next question

Textbooks

High-yield textbook

Extended textbook

Media

PassMedicine

Question 251 of 414 ✗

An 18-year-old man presents to the nurse at the local health centre with a third episode of balanitis over the past 3 months. He also has vague symptoms of tiredness. His father and grandfather were diagnosed with type 1 diabetes and take a basal-bolus insulin regimen. He is slim with a body mass index of 22 kg/m^2. He is noted to have glycosuria on urine dipstick testing.

A fasting blood sample shows the following:

Na^+	140 mmol/l
K^+	3.9 mmol/l
Urea	6.1 mmol/l
Creatinine	91 µmol/l
Glucose	9.2 mmol/l

Which of the following is the most likely diagnosis?

	Latent autoimmune diabetes of adults (LADA)	13%
🟩	Maturity onset diabetes of the young (MODY)	66%
	Renal glycosuria	3%
	Type 1 diabetes	18%
🟥	Type 2 diabetes	1%

MODY is autosomal dominant diabetes mellitus which often presents for the first time in young slim individuals without symptoms of polyuria and polydipsia. Insidious onset with for instance with recurrent balanitis as here is usual. It's important to recognise the diagnosis because many patients with MODY including those with the HNF-1 alpha form of the disease can be managed with sulphonylureas for many years before needing to start insulin therapy. Evaluation of family history and testing for antibodies for type 1 diabetes can help to differentiate MODY from other forms of diabetes mellitus.

Type 1 diabetes isn't associated with such strong heritability as that seen here, and given this patient's body habitus, type 2 diabetes is very unlikely. LADA is associated with a body habitus similar to the overweight / obese picture seen in type 2 diabetes for many patients, although progression to insulin therapy occurs more quickly. Renal glycosuria is ruled out by the elevated fasting glucose seen here.

👍 👎 Discuss (12) Improve

Next question

MODY ★

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes, typically characterized by an autosomal dominant inheritance pattern, onset usually before 25 years of age, and impairment in insulin secretion with minimal or no defects in insulin action. Unlike more common forms of diabetes, such as Type 1 and Type 2, MODY is not primarily driven by lifestyle factors.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

Classification and Genetics

MODY is a heterogenous group, with over 14 types identified as of the latest revision, each corresponding to mutations in different genes. The most common types are MODY2 (GCK mutation) and MODY3 (HNF1A mutation), but others include MODY1 (HNF4A), MODY4 (PDX1), MODY5 (HNF1B), and so on.

MODY 3 accounts for around 60% of cases with MODY 2 causing 20% of cases.

Each subtype varies in its clinical presentation, management, and prognosis, emphasizing the importance of precise genetic diagnosis in order to guide treatment strategy and genetic counselling.

Clinical Features

Patients with MODY often present with mild non-ketotic hyperglycemia that is often detected incidentally or during routine screening. It may also be discovered during pregnancy. Unlike Type 1 diabetes, patients with MODY usually do not present with diabetic ketoacidosis except under severe stress conditions, and unlike Type 2 diabetes, they are often of normal weight and do not exhibit signs of insulin resistance.

The specific clinical manifestations and complications can vary depending on the subtype of MODY. For example, individuals with MODY2 generally have mild, stable fasting hyperglycemia and rarely develop severe complications, whereas those with MODY3 or MODY1 may have progressive hyperglycemia and are at higher risk for complications typically associated with diabetes, such as retinopathy, nephropathy, and cardiovascular disease.

Diagnosis

MODY should be suspected in individuals with persistent, asymptomatic hyperglycemia detected before the age of 25, without the typical features of Type 1 or Type 2 diabetes.

The diagnosis is confirmed by genetic testing, which is crucial for identifying the specific type of MODY, as this has direct implications for management. It's important to remember, however, that genetic testing can be expensive and may not be available in all settings.

Treatment

The treatment for MODY depends on the specific genetic subtype. For example, MODY2 often does not require specific treatment, as the hyperglycemia is mild and usually does not lead to complications. In contrast, MODY associated with HNF1A often respond well to treatment with low-dose sulfonylureas. Insulin therapy may be necessary in some cases, especially during pregnancy or if sulfonylureas are contraindicated or ineffective.

Next question

B *I* A T↕

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Question 252 of 414 ✓

A 19-year-old female with a history of anorexia nervosa is admitted to hospital. Her BMI has dropped to 16. She has agreed to be fed by nasogastric tube. Which one of the following electrolyte disturbances is most likely to occur?

Hyperkalaemia	6%
Hypocalcaemia	6%
Metabolic acidosis	4%
Hypophosphataemia	79%
Hypermagnesemia	4%

Refeeding syndrome causes hypophosphataemia

Important for me Less important

This patient is at risk of refeeding syndrome, which can lead to profound hypophosphataemia

Discuss (2) Improve

Next question

Hypophosphataemia

Causes
- alcohol excess
- acute liver failure
- diabetic ketoacidosis
- refeeding syndrome
- primary hyperparathyroidism
- osteomalacia

Consequences

- red blood cell haemolysis
- white blood cell and platelet dysfunction
- muscle weakness and rhabdomyolysis
- central nervous system dysfunction

Next question

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Media

Hypophosphataemia

Osmosis - YouTube 👍 2 👎 0

Report broken media

Score: **23.4%**

1 ✓

2 ✓

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Question 253 of 414 ✓

A 61-year-old woman is investigated for hoarseness and dyspnoea which has got progressively worse over the past month. In the past she has been diagnosed with toxic multinodular goitre which was successfully treated with radioiodine. On examination she has a firm, asymmetrical swelling of the thyroid gland. Laryngoscopy demonstrates a right vocal cord paralysis and apparent external compression of the trachea. What is the most likely diagnosis?

Follicular thyroid cancer	9%
Papillary thyroid cancer	14%
Medullary thyroid cancer	11%
Lymphoma of the thyroid gland	9%
Anaplastic thyroid cancer	57%

Anaplastic thyroid cancer - aggressive, difficult to treat and often causes pressure symptoms

Important for me Less important

The correct answer is **Anaplastic thyroid cancer**. Anaplastic thyroid cancer is a rare, aggressive type of thyroid cancer that typically presents with rapidly enlarging neck mass, hoarseness, and dyspnoea due to compression of the trachea and laryngeal nerve involvement. The patient's history of toxic multinodular goitre treated with radioiodine may have increased her risk for developing anaplastic thyroid cancer. Additionally, the presence of vocal cord paralysis and external compression of the trachea on laryngoscopy support this diagnosis.

Follicular thyroid cancer is a less aggressive form of thyroid cancer that usually presents as a solitary nodule within the gland. Although it can cause hoarseness and dyspnoea if it invades the surrounding structures, it typically does not present with such rapid progression or significant compressive symptoms as seen in this case.

Papillary thyroid cancer is the most common type of thyroid cancer but tends to be slow-growing and less aggressive than anaplastic thyroid cancer. It often presents as a painless nodule in the neck without significant compressive symptoms. While papillary carcinoma can present with vocal cord paralysis due to recurrent laryngeal nerve invasion, its relatively indolent nature makes it less likely in this case with rapidly progressing symptoms.

Medullary thyroid cancer arises from parafollicular C cells and can be associated with multiple endocrine neoplasia (MEN) syndromes. Patients may present with a neck mass, but medullary carcinoma typically does not cause compressive symptoms like hoarseness or dyspnoea unless it has metastasized to regional lymph nodes. Additionally, patients often have elevated calcitonin levels which can aid in diagnosis.

Lastly, **Lymphoma of the thyroid gland** is a rare malignancy that can present with a rapidly enlarging neck mass, hoarseness, and dyspnoea. However, it is more commonly seen in patients with a history of Hashimoto's thyroiditis rather than toxic multinodular goitre. Furthermore, the presence of vocal cord paralysis makes anaplastic thyroid cancer more likely in this case.

In summary, the patient's rapid progression of symptoms, compressive findings on laryngoscopy, and history of toxic multinodular goitre treated with radioiodine make anaplastic thyroid cancer the most likely diagnosis.

👍 👎 Discuss (4) Improve

Next question

Thyroid cancer ★

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's thyroiditis

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	• Usually contain a mixture of papillary and colloidal filled follicles • Histologically tumour has papillary projections and pale empty nuclei • Seldom encapsulated • Lymph node metastasis predominate • Haematogenous metastasis rare
Follicular adenoma	• Usually present as a solitary thyroid nodule • Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. • Vascular invasion predominates • Multifocal disease raree
Medullary carcinoma	• C cells derived from neural crest and not thyroid tissue • Serum calcitonin levels often raised • Familial genetic disease accounts for up to 20% cases • Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.
Anaplastic carcinoma	• Most common in elderly females • Local invasion is a common feature • Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

Next question

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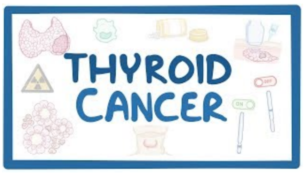
Links

British Thyroid Association 👍 3 👎 3

2014 Guidelines for the Management of Thyroid Cancer

Report broken link

Media



Thyroid cancer

Osmosis - YouTube 👍 20 👎 1

Thyroid Nodule

Armando Hasudungan - YouTube 👍 12 👎 4

Report broken media

Score: **23.7%**

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Question 254 of 414 ✓

A 54-year-old man was referred to the acute medical unit as his blood test results were concerning. He noted that he was feeling slightly nauseous at home and was generally slightly tired. Apart from this, he remained otherwise well with no other systemic complaints. He recalls that he was recently started on a new medication by his GP but could not recall the name of the medication.

He reports drinking up to 3L water in a day but states this is normal for him. Physical examination was unremarkable. Skin turgor is normal and oral mucous membranes are moist. Heart rate was at 80 beats/minute and blood pressure was at 110/60mmHg.

Blood tests were repeated in hospital and the results were as below:

Blood test	Result at GP practice	Repeat result today	Normal range
Na^+	127 mmol/L	125mmol/L	(135 - 145)
K^+	3.6 mmol/L	3.7mmol/L	(3.5 - 5.0)
Urea	6.5 mmol/L	6.0 mmol/L	(2.0 - 7.0)
Creatinine	110 µmol/L	105 µmol/L	(55 - 120)

Further tests were carried out and the results were as below:

Random cortisol	450nmol/L	>350nmol/L
Thyroid-stimulating hormone (TSH)	4.5 mU/L	(0.5-5.5)
Plasma osmolality	255 mOsm/kg	285-295
Urine osmolality	525mOsm/kg	50-1200 mOsm/kg
Urinary sodium	40 mOsm/kg	<20mOsm/kg

Given the likely diagnosis, which of the following could be the cause for his deranged blood tests?

Amoxicillin	1%
Lithium	37%
Sertraline	46%
Bisoprolol	

Bisoprolol	1%
Spironolactone	15%

SIADH - drug causes: carbamazepine, sulfonylureas, SSRIs, tricyclics

Important for me Less important

Given the patient's blood tests, it is most likely that his hyponatremia is driven by a syndrome of inappropriate ADH (SIADH). This is evidenced by the low plasma osmolality with the inappropriately elevated urine osmolality and raised urine sodium.

While the urine osmolality remains within the normal limits, this is interpreted with the plasma osmolality. Given the low plasma osmolality, the urine osmolality would be expected to be either similar or lower than the plasma osmolality as the body attempts to excrete water. However, given that the urine osmolality is higher than the plasma osmolality, this suggests that urine is being inappropriately concentrated.

The next key issue is to identify the likely cause from the list given and sertraline is the most likely cause in this case. It is important to note that most antidepressants have the ability to cause hyponatremia and needs to be kept in mind.

Spironolactone would be another medication that can cause hyponatremia but its underlying mechanism of action would be via the blockade of the eNAC channel rather than via the SIADH pathway. Blood tests would typically show a rising plasma osmolality rather than a low plasma osmolality. Also, the patient would be expected to be hypovolemic due to the diuretic effect of spironolactone.

Lithium would cause diabetes insipidus rather than SIADH. This would present with increased urine output, low urine osmolality and raised plasma osmolality. This is opposite to the results provided. Hypernatremia is also normally expected rather than hyponatremia.

Bisoprolol and amoxicillin are not known to cause issues with sodium levels.

👍 👎 Discuss (7) Improve

Next question

Syndrome of inappropriate ADH secretion ★

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention. Patients with SIADH are typically euvolemic, i.e. they do not show signs of overt volume depletion or overload.

Pathophysiology

- SIADH involves an excessive release of antidiuretic hormone (ADH), also known as vasopressin, which leads to water retention, volume expansion, and dilutional hyponatraemia
- ADH is produced by the hypothalamus and stored in the posterior pituitary gland. Its primary function is to regulate the body's water balance
- It does this by increasing water reabsorption in the collecting ducts of the kidneys, thereby decreasing the volume of urine produced
- In SIADH, there is an inappropriate and continuous release of ADH that is not inhibited by normal physiological mechanisms, such as adequate or excess body fluid levels
- As a result, the kidneys reabsorb more water, leading to decreased urine output, and expansion of extracellular fluid volume.
- Importantly, this increase in body fluid volume does not lead to the expected signs of fluid overload, such as oedema or hypertension, because the excess fluid is uniformly distributed throughout all body fluid compartments.
- However, as water is retained in the body, the concentration of electrolytes in the blood, particularly sodium, becomes diluted, leading to hyponatraemia.

Causes of SIADH

Category	**Examples**
Malignancy	• **small cell lung cancer** • also: pancreas, prostate
Neurological	• stroke • subarachnoid haemorrhage • subdural haemorrhage • meningitis/encephalitis/abscess
Infections	• tuberculosis • pneumonia
Drugs	• sulfonylureas* • SSRIs, tricyclics • carbamazepine • vincristine

Category	Examples
	• cyclophosphamide
Other causes	• positive end-expiratory pressure (PEEP) • porphyrias

Investigations

- Urine osmolality: Urine osmolality is inappropriately high (>100 mOsm/kg) in relation to serum osmolality, as the kidneys should normally dilute urine in the setting of low serum osmolality.
- Urine sodium concentration: Urine sodium concentration is typically high (>40 mmol/L) due to the action of ADH on the renal tubules.

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

Next question

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Question 255 of 414 ✓

A 28-year-old woman with polycystic ovarian syndrome consults you as she is having problems becoming pregnant. She has a past history of oligomenorrhea and has previously recently stopped taking a combined oral contraceptive pill. Despite stopping the pill 6 months ago she is still not having regular periods. Her body mass index is 28 kg/m^2. Apart from advising her to lose weight, which one of the following interventions is most effective in increasing her chances of conceiving?

Metformin	21%
Bromocriptine	1%
Laparoscopic ovarian cautery	1%
[✓ Clomifene]	75%
Orlistat	1%

Infertility in PCOS - clomifene is typically used first-line

Important for me Less important

Whilst metformin has a role in the management of infertility it should be used second-line to anti-oestrogens such as clomifene. Similar questions to this often appear in which clomifene is not an option, in this case metformin is clearly the right answer.

Discuss (2) Improve

Next question

Polycystic ovarian syndrome: management

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

General

- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne

- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility

- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

Next question

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Links

RCOG 👍 4 👎 0

Opinion paper on metformin in PCOS

ESHRE (European Society of Human Reproduction and Embryology) 👍 1 👎 0

2018 International Evidence Based Guideline for the Assessment and Management of PCOS

Patient.info 👍 1 👎 0

Polycystic ovarian syndrome review

Clinical Knowledge Summaries 👍 3 👎 1

Polycystic ovarian syndrome

Royal College of Obstetricians and Gynaecologists 👍 2 👎 1

2014 Long-term Consequences of Polycystic Ovary Syndrome

NEJM 👍 1 👎 1

Summary of recent trial comparing metformin to clomifene

Report broken link

Score: **24.3%**

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Question 256 of 414 ✓

A 41-year-old man presents with recurrent headaches. These typically occur 2-3 times a day and are associated with sweating and palpitations. As he was concerned that it may be due to blood pressure he borrowed his fathers home monitor. During these episodes his blood pressure is around 210/110 mmHg. Given the likely diagnosis, what is the most appropriate next test?

MRI adrenals	3%
Phenoxybenzamine suppression test	1%
24 hour urinary collection of vanillylmandelic acid	9%
[✓ 24 hour urinary collection of metanephrines]	68%
24 hour urinary collection of catecholamines	19%

Phaeochromocytoma: do 24 hr urinary metanephrines, not catecholamines

Important for me Less important

Three 24 hour collections are needed as some patients have intermittently raised levels.

Discuss (6) Improve

Next question

Phaeochromocytoma ★

Phaeochromocytoma is a rare catecholamine secreting tumour. About 10% are familial and may be associated with MEN type II, neurofibromatosis and von Hippel-Lindau syndrome

Basics

- bilateral in 10%
- malignant in 10%
- extra-adrenal in 10% (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)

Features are typically episodic

- hypertension (around 90% of cases, may be sustained)
- headaches
- palpitations
- sweating
- anxiety

Tests

- 24 hr urinary collection of metanephrines (sensitivity 97%*)
- this has replaced a 24 hr urinary collection of catecholamines (sensitivity 86%)

Surgery is the definitive management. The patient must first however be stabilized with medical management:

- alpha-blocker (e.g. phenoxybenzamine), given before a
- beta-blocker (e.g. propranolol)

*BMJ 2012; 344 doi: http://dx.doi.org/10.1136/bmj.e1042 (Published 20 February 2012)

Next question

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Links

Postgraduate Medical Journal 👍 2 👎 3

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Question 257 of 414 ✗

A 53-year-old man is seen in the endocrinology clinic with a 6-month history of weight gain. He also complains of excessive sweating and oily skin. There have been no recent changes to his diet and there is no history of recent illness. He has a past medical history of chronic pancreatitis and takes no regular medications.

His observations are as follows:

- Temperature 36.2 °C
- Heart rate 90bpm
- Blood pressure 158/90mmHg
- Respiratory rate 16 breaths/min
- Oxygen saturations 98% on room air

On examination, he has a protruding jaw and widened interdental spaces. Cardiovascular and abdominal examinations are unremarkable.

Given the likely diagnosis, what is the most initial investigation to consider?

	Faecal elastase	1%
🟥	Growth hormone levels	10%
	MRI pituitary gland	4%
	Oral glucose tolerance test	9%
🟩	Serum IGF-1 levels	76%

Serum IGF-1 levels are now the first-line test for acromegaly

Important for me Less important

This patient has symptoms of acromegaly including weight gain, increased sweating and changes to his physical appearance such as prognathism and likely increase in shoe size. Currently, NICE guidelines recommend that the first-line investigation for acromegaly is to test serum IGF-1 levels. It correlates well with growth hormone levels and has a longer half-life. Serum IGF-1 levels are highly sensitive. Therefore, a normal result can exclude acromegaly.

Faecal elastase is used to assess for exocrine deficiency in patients with chronic pancreatitis. However, this patient is presenting with symptoms of acromegaly, for which, faecal elastase is not used in the diagnosis.

Serum growth hormone levels are not recommended routinely. This is because their release is episodic with a short half-life and is more likely to give inaccurate measurements.

An MRI of the pituitary gland is warranted to exclude a pituitary adenoma causing excess growth hormone release. However, it is not the most initial test to consider. Furthermore, without the presence of headache or visual symptoms (commonly bitemporal hemianopia), an MRI pituitary gland would be not indicated at this stage.

An oral glucose tolerance test has now become the confirmatory investigation and is used **after** serum IGF-1 levels return as being raised. Glucose normally inhibits the release of growth hormone. Therefore, if a positive growth hormone level is achieved after a glucose challenge, acromegaly can be confirmed.

👍 👎 Discuss (2) Improve

Next question

Acromegaly: investigations ★

Growth hormone (GH) levels vary during the day and are therefore not diagnostic.

Serum IGF-1 levels have now overtaken the oral glucose tolerance test (OGTT) with serial GH measurements as the first-line test. The OGTT test is recommended to confirm the diagnosis if IGF-1 levels are raised.

The Endocrine Society guidelines suggest the following:

> *1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features.*
> ...
> *1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of*

> *the diagnosis by finding lack of suppression of GH to < 1 µg/L following documented hyperglycemia during an oral glucose load.*

Serum IGF-1 may also be used to monitor disease

Oral glucose tolerance test

- in normal patients GH is suppressed to < 2 mu/L with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour.

Next question

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Links

The Endocrine Society 👍 8 👎 0

2014 Acromegaly guidelines

Report broken link

Media

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Question 258 of 414 ✗

A 42-year-old woman is seen in the clinic as part of an occupational health check. As part of the check, she has a random glucose test taken which is found to be slightly raised. The patient has a raised BMI of 39 kg/m^2 but is otherwise well and is not on any regular medications.

The patient is keen to avoid regular medications and therefore a plan is agreed for her to trial dietary adjustments. She is provided with dietary advice including the avoidance of food type with a high glycaemic index. She is booked to undergo formal glucose testing in a few weeks time.

What food example should this patient avoid?

Boiled new potatoes	9%
Brown rice	3%
Digestive biscuits	8%
🟥 Peanuts	2%
🟩 White bread	79%

White bread is an example of a high glycaemic index food

Important for me Less important

White bread is known to have a high glycaemic index (GI) with a score of 80/100, well above the 70/100 level to be considered a high GI food. The GI of a specific food is based primarily on the amount and type of carbohydrate present and can be affected by the cooking method, processing and in the context of fruit the ripeness of the food (riper fruits contain more sugars and therefore a higher GI).

Boiled new potatoes are considered to have a medium GI with a score of 62/100. Unlikely baked potatoes, which are considered to have a high GI, they do not necessarily have to be avoided.

Brown rice is considered to have a medium GI with a score of 58/100. Brown rice is recommended as an alternative to white rice which does have a high GI score of 87/100.

Digestive biscuits although commonly thought to be high in sugar, have a GI score of only

59/100 and therefore are considered to have a medium GI score.

Peanuts are low in carbohydrate level and therefore have a low GI score.

👍 👎 Discuss (1) Improve

Next question

Glycaemic index ★

The glycaemic index (GI) describes the capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals. Foods with a high GI may be associated with an increased risk of obesity and the post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

Classification	Examples
High GI	White rice (87), baked potato (85), white bread (80)
Medium GI	Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58), Porridge (55)
Low GI	Fruit and vegetables, peanuts

The glycaemic index is shown in brackets. Glucose, by definition, would have a glycaemic index of 100

Next question

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Question 259 of 414 ✗

You have been asked to review a 52-year-old woman in the emergency department with dyspnoea accompanied by nausea and vomiting. She tells you that she initially attributed this to a flu-like illness but as she found herself becoming increasingly short of breath she was taken to hospital by her concerned husband. Her past medical history is significant for type 2 diabetes mellitus, hypertension and obesity. Her current medications include metformin 1gram bd, canagliflozin 100mg od, ramipril 10mg od and amlodipine 5mg od. On examination she has a respiratory rate of 25 breaths/min, blood pressure 130/67 mmHg, pulse 105 bpm and oxygen saturation of 98% on room air. The only finding you elicit on physical examination is mild tenderness in the epigastric area. Her ECG shows a sinus tachycardia. Routine blood results are shown below:

Hb	167 g/l	Na^+	132 mmol/l	Bilirubin	22 µmol/l	pH	7.14
Platelets	$410 * 10^9$/l	K^+	5.5 mmol/l	ALP	100 u/l	PaO_2	12 KPa
WBC	$11.2 * 10^9$/l	Urea	10.4 mmol/l	ALT	55 u/l	$PaCO_2$	1.9 KPa
Neuts	$10.0 * 10^9$/l	Creatinine	111 µmol/l	γGT	23 u/l	HCO_3^-	11µmol/l
Lymphs	$1.1 * 10^9$/l	Amylase	321 U/l	Albumin	33 g/l	Lactate	3.0 mmol/l
Eosin	$0.1 * 10^9$/l	Cl^-	101 mmol/l	Urine	Ketones 3+	Glucose	11mmol/L

What is the most likely diagnosis?

	Small bowel obstruction	1%
🟥	Metformin induced lactic acidosis	20%
	Starvation ketosis	4%
🟩	Euglycaemic diabetic ketoacidosis	64%
	Pancreatitis	11%

This lady has euglycaemic diabetic ketoacidosis (EuDKA) secondary to her sodium-glucose co-transporter 2 (SGLT2) inhibitor, canagliflozin. EuDKA is an important to recognise side effect of this novel class of oral hypoglycaemic agents and should be thought of in any patient with an unexplained raised anion gap acidosis and normal blood sugar level who is on one of these medications.

Exactly how these agents cause EuDKA has yet to be determined. However, it is hypothesised that as these agents lower blood sugar levels by increasing the excretion of glucose the resulting reduction in plasma glucose results in reduced insulin secretion from pancreatic beta-cells and these patients entering a state of relative insulin deficiency. This leads to a lowering of the antilipolytic activity of insulin, and the consequent stimulation of the production of free fatty acids, which are then converted to ketone bodies by beta-oxidation in the liver. Moreover, insulin stimulates the activity of acetyl-CoA carboxylase, which produces malonyl-CoA, a potent inhibitor of carnitine palmitoyltransferase (CPT-I). Given that CPT-I promotes the transport of fatty acids into mitochondria and hence increases the rate of beta-oxidation, the decrease in the circulating level of insulin promotes the production of ketone bodies through activation of CPT-I.

👍 👎 Discuss (9) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include

- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

PassMedicine

Question 260 of 414 ✗

A 45-year-old male is investigated for polyuria. A water deprivation test is done to ascertain the cause.

Water deprivation started at 8 am.

Plasma osmolality after 8 hours	305 mOsm/kg
Urine osmolality after 8 hours	190 mOsm/kg
Urine osmolality after 4 hours after desmopressin	575 mOsm/kg

Based on the presumed diagnosis, what feature is this patient most likely to have in their past medical history?

	A recent acute kidney injury (AKI)	4%
	Concurrent lithium use	20%
	Primary hyperparathyroidism	5%
🟩	Recent transsphenoidal pituitary surgery	66%
🟥	Schizophrenia	5%

Water deprivation test: cranial DI

- urine osmolality after fluid deprivation: low
- urine osmolality after desmopressin: high

Important for me Less important

This is a case of cranial diabetes insipidus. Despite 8 hours of water deprivation, the patient's urine is still incredibly dilute suggesting a water concentration issue with vasopressin. The fact that the urine osmolality increments wonderfully with desmopressin, it suggests that there is a vasopressin production issue, implying cranial diabetes insipidus.

Recent transsphenoidal is a well-documented cause for cranial diabetes insipidus and would be most relevant given the water deprivation findings above.

Now to look at the other options.

Recent AKI would be important in the polyuric phase of an AKI, however, these results suggest a vasopressin issue given the marked response to desmopressin.

Concurrent lithium use is relevant for nephrogenic diabetes insipidus.

Primary hyperparathyroidism with subsequent hypercalcaemia is another well-documented cause for nephrogenic diabetes insipidus.

Schizophrenia is one of the most common associations with psychogenic (primary) polydipsia.

👍 👎 Discuss (2) Improve

Next question

Water deprivation test ★

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	**Final urine osm.**	**Urine osm. post-DDAVP**
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

Textbooks

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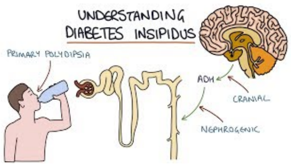
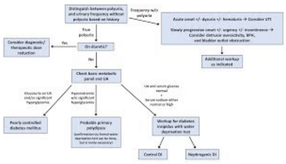
Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5



An Approach to Polyuria

Strong Medicine - YouTube 👍 29 👎 4

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Score: **24.2%**

1 ✓
2 ✓
3 ✓

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Question 261 of 414 ✗

An 18-year-old girl is admitted to the Emergency Department with an episode of sweating and dizziness. She is brought in by her father who has type 2 diabetes mellitus as he is worried she may be diabetic. He describes a number of similar episodes for the past two weeks. Her BM on admission is 1.9 mmol/l so the following bloods are taken:

Plasma glucose	1.8 mmol/l
Insulin	15 mg/ml (6-10 mg/ml)
Proinsulin	22% (22-24%)
C-peptide	0.15 nmol/l (0.2-0.4 nmol/l)

What is the most likely diagnosis?

	Diabetes mellitus	2%
🟥	Insulinoma	29%
	Nesidioblastosis	2%
🟩	Insulin abuse	58%
	Sulfonylurea abuse	9%

The raised insulin with low c-peptide level points to a diagnosis of insulin abuse. C-peptide levels would be raised in a patient following sulfonylurea abuse

Discuss (12) Improve

Next question

Hypoglycaemia

Causes

- insulinoma - increased ratio of proinsulin to insulin

- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
    - causes exaggerated insulin secretion
    - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia

- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
    - Sweating
    - Shaking
    - Hunger
    - Anxiety
    - Nausea
- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
    - Weakness
    - Vision changes
    - Confusion
    - Dizziness
- Severe and uncommon features of hypoglycaemia include:
    - Convulsion
    - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):

    - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
    - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
    - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
    - If the patient is alert, a quick-acting carbohydrate may be given (as above)
    - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
    - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

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Links

Postgraduate Medical Journal

Review of endocrine emergencies

👍 12 👎 2

Report broken link

Score: **24.1%**

1 ✓

2 ✓

PassMedicine

← Question 262 of 414 ✗ ⚐ →

A 45-year-old man with a history of depression and gastro-oesophageal reflux disease presents due to a milky discharge from his nipples. The following blood results are obtained:

Prolactin	700 mu/l

Which one of his medications is most likely to be responsible?

Omeprazole	3%
Fluoxetine	11%
🟩 Metoclopramide	59%
🟥 Cimetidine	21%
Amitriptyline	6%

Causes of raised **p**rolactin - the **p**'s

- **p**regnancy
- **p**rolactinoma
- **p**hysiological
- **p**olycystic ovarian syndrome
- **p**rimary hypothyroidism
- **p**henothiazines, metoclo**p**ramide, dom**p**eridone

Important for me Less important

Selective serotonin reuptake inhibitors such as fluoxetine have rarely been associated with hyperprolactinaemia but the most likely cause in this patient is metoclopramide. Cimetidine is generally associated with gynaecomastia, rather than galactorrhoea.

Discuss (7) Improve

Next question

Prolactin and galactorrhoea

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. Dopamine acts as the primary prolactin releasing inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- prolactinoma
- pregnancy
- oestrogens
- physiological: stress, exercise, sleep
- acromegaly: 1/3 of patients
- polycystic ovarian syndrome
- primary hypothyroidism (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- metoclopramide, domperidone
- phenothiazines
- haloperidol
- very rare: SSRIs, opioids

Next question

Textbooks

PassMedicine

← Question 263 of 414 ✕ ⚐ →

A 62-year-old woman presents with a several-year history of urinary leakage that occurs when she coughs or sneezes. It has gradually worsened over time and is becoming increasingly embarrassing. She denies any episodes occurring outside of these events and has no significant past medical history. Examination is unremarkable. The patient has tried pelvic floor muscle training but this has not been effective. She is not keen on surgical intervention.

What is the best next step in management?

	Botulinum toxin	2%
🟩	Duloxetine	73%
	Mirabegron	10%
🟥	Oxybutynin	12%
	Tolterodine	2%

Duloxetine may be used in patients with stress incontinence who don't respond to pelvic floor muscle exercises and decline surgical intervention

Important for me Less important

This patient is experiencing stress incontinence, given the triggers of coughing and sneezing. Laughing is also a common trigger. Pelvic floor exercises are the first-line option for management. Women may then be referred for surgical procedures, such as retropubic mid-urethral tape procedures. However, if they decline surgical intervention, **duloxetine** can be offered and can be significantly beneficial.

Botulinum toxin may be injected into the bladder if pharmacotherapy for urge incontinence is unsuccessful. Urge incontinence instead presents with a sudden urge to urinate, followed by uncontrollable leakage. It is important to remember that patients may have a mixed pattern of incontinence.

Mirabegron is a beta-3 agonist and may be used to manage urge incontinence, not stress incontinence. It is particularly useful in the elderly, with whom anticholinergic side effects from other drugs may be of concern.

Oxybutynin is used to manage urge, rather than stress, incontinence. It should be avoided in frail, older women due to the increased risk of falls.

Tolterodine is also used in urge incontinence, not stress incontinence. It is sometimes used as an alternative to oxybutynin in older women.

👍 👎 Discuss Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation
- bladder diaries should be completed for a minimum of 3 days

- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

High-yield textbook

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Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

Report broken link

Media

URINARY INCONTINENCE

Urinary incontinence

Osmosis - YouTube 👍 0 👎 1

Report broken media

Score: **24%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗

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Question 264 of 414 ✗

A 19-year-old woman attends the nephrology clinic due to suspected Bartter's syndrome because of chronic hypokalaemia causing muscle spasms. She reports polydipsia. There is no significant family history.

On exam, she is short, her blood pressure is 114/65 mmHg, her heart rate is 65bpm and has no skeletal deformities.

Her blood and urinalysis show:

Na^+	145 mmol/L	(135 - 145)
K^+	2.9 mmol/L	(3.5 - 5.0)
Bicarbonate	34 mmol/L	(22 - 29)
Urea	6.5 mmol/L	(2.0 - 7.0)
Creatinine	70 μmol/L	(55 - 120)
Renin	58 pmol/mL/h	(5.4 - 30)
Aldosterone	678 pmol/L	(100 - 450)
Urinary Ca^{2+}	9.8 mmol/24 h	(2.50 - 7.50)

What is the pathophysiology of this presentation?

	Carbonic anhydrase inhibition	2%
🟥	Continuous activation of epithelial sodium channels (ENaC) in the collecting duct	6%
	Defect of proximal bicarbonate and electrolyte reabsorption	4%
🟩	Defective NKCC2 channel in the ascending loop of Henle	81%
	Defective NaCl channel in the distal convoluted tubule	7%

Bartter's syndrome results from a defective NKCC2 channel in the ascending loop of Henle

Important for me Less important

Bartter's syndrome is an autosomal recessive condition where a **defective NKCC2 channel in the ascending loop of Henle** causes persistent hypokalaemia in the setting of metabolic alkalosis. Common clinical features are short stature, polydipsia, polyuria, and nocturia. Patients are typically normotensive in the setting of elevated renin and aldosterone. Treatment involves potassium supplementation and potassium-sparing diuretics such as spironolactone and amiloride. A distinguishing feature in Bartter's syndrome compared to Gitelman's syndrome is hypercalciuria.

Carbonic anhydrase plays an important role in the proximal tubule in bicarbonate, sodium, and chloride reabsorption. **Carbonic anhydrase inhibition** leads to sodium, chloride and bicarbonate loss. Carbonic anhydrase inhibition-induced diuresis is usually modest as most of the excess fluid delivered out of the proximal tubule is reclaimed in the more distal nephron segments. Acetazolamide inhibits carbonic anhydrase and is used for glaucoma, diuretic-resistant heart failure, and altitude sickness.

Liddle syndrome is an autosomal dominant condition where there is **continuous activation of epithelial sodium channels (ENaC) in the collecting duct**. This leads to hypokalemia and metabolic alkalosis but in the setting of hypertension and low renin and aldosterone. Treatment involves medications that block ENaC and decrease sodium reabsorption such as amiloride.

A **defect of proximal bicarbonate and electrolyte reabsorption** is seen in renal tubular acidosis (RTA) type 2. Causes of RTA type 2 include Sjogren's syndrome, amyloidosis, and Fanconi syndrome. Fanconi syndrome can occur as an inherited or acquired condition. Acquired causes of Fanconi included medication-induced such as gentamicin and azathioprine.

Gitelman syndrome is an autosomal recessive condition where there is a **defective sodium-chloride co-transporter in the distal tubule** like the mechanism of action of thiazide diuretics. Patients are usually either normotensive or borderline hypotensive. Hypokalaemia and metabolic alkalosis are present similar to Bartter's syndrome but hypocalciuria is present instead.

👍 👎 Discuss (1) Improve

Next question

Bartter's syndrome ★

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na^+ K^+ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

Next question

Textbooks

High-yield textbook

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Links

Royal College of Physicians 👍 9 👎 3

2012 Renal tubular disorders review

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Score: **23.9%**

1 ✓

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Question 265 of 414 ✗

What is the mechanism of action of exenatide?

	Glucagon inhibitor	2%
	Dipeptidyl peptidase-4 (DPP-4) inhibitor	7%
🟩	Glucagon-like peptide-1 (GLP-1) mimetic	83%
🟥	Incretin inhibitor	5%
	Alpha-glucosidase inhibitor	2%

Exenatide = Glucagon-like peptide-1 (GLP-1) mimetic

Important for me Less important

Discuss (2) Improve

Next question

Diabetes mellitus: GLP-1 drugs

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

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Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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Media

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Question 266 of 414 ✓

An elderly male of no fixed abode with a history of alcohol dependency and chronic liver disease is taken to the Emergency Department with reduced consciousness (GCS 5) and a blood glucose of 1.3 mmol/L.

What is the correct management of his hypoglycaemia?

IM Glucagon STAT	33%
Lucozade	1%
100ml IV Normal Saline	1%
100ml IV Dextrose 5%	10%
100ml IV Glucose 20%	55%

Hypoglycaemia in patients with alcoholic liver disease does not respond to glucagon

Important for me Less important

Patients with alcoholic liver disease have depleted glycogen stores, therefore, treatment with glucagon does not improve blood glucose.

It is not safe to use the oral route when the patient is GCS 5, therefore, administering Lucozade is not appropriate.

Normal saline does not correct hypoglycaemia.

5% dextrose is a maintenance fluid and not appropriate for acute treatment of hypoglycaemia.

Therefore, the correct answer is 100ml IV Glucose 20%.

Discuss (7) Improve

Next question

Hypoglycaemia ★

Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
  - causes exaggerated insulin secretion
  - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia

- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
  - Sweating
  - Shaking
  - Hunger
  - Anxiety
  - Nausea
- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
  - Weakness
  - Vision changes
  - Confusion
  - Dizziness
- Severe and uncommon features of hypoglycaemia include:
  - Convulsion

  - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):
  - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
  - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
  - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
  - If the patient is alert, a quick-acting carbohydrate may be given (as above)
  - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
  - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

Textbooks

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Links

Postgraduate Medical Journal 👍 12 👎 2

Review of endocrine emergencies

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← Question 267 of 414 ✗ ⚐ →

A 43-year-old man has a routine medical for insurance purposes. The following result is obtained:

Uric acid	622 μmol/l (210 - 480)

He is well with no significant past medical history. What is the most appropriate test to perform next?

🟩	Lipid profile	36%
	Thyroid function test	9%
	Calcium	15%
	Parathyroid hormone	13%
🟥	Pyrophosphate levels	27%

Hyperuricaemia may be associated with both hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

👍 👎 Discuss (8) Improve

Next question

Hyperuricaemia ★

Increased levels of uric acid may be seen secondary to either increased cell turnover or reduced renal excretion of uric acid. Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout

Hyperuricaemia may be associated with hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Increased synthesis

- Lesch-Nyhan disease

- Lesch-Nyhan disease
- myeloproliferative disorders
- diet rich in purines
- exercise
- psoriasis
- cytotoxics

Decreased excretion

- drugs: low-dose aspirin, diuretics, pyrazinamide
- pre-eclampsia
- alcohol
- renal failure
- lead

Next question

Textbooks

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Media

LESCH-NYHAN SYNDROME
Osmosis.org

Lesch-Nyhan syndrome

Osmosis - YouTube 👍 12 👎 1

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Question 268 of 414 ✓

A 55-year-old woman presents with a 1-year history of involuntary urine leakage when she sneezes or coughs. This has caused significant embarrassment and she now wears continence pads whenever she goes out.

She denies urinary urgency or frequency and opens her bladder once at night. She has no bowel-related symptoms.

She has tried pelvic floor exercises with support from a women's health physiotherapist for the past 6 months but still finds the symptoms very debilitating. She is keen to try further treatment, although is frightened by the prospect of surgery and would prefer alternative measures.

Urinalysis is unremarkable. On vaginal examination, there is no evidence of pelvic organ prolapse.

What is the next most appropriate treatment?

Offer a ring pessary	4%
Offer a trial of duloxetine	75%
Offer a trial of oxybutynin	15%
Refer to continence nurse for bladder training	3%
Advise continuing pelvic floor exercises for a further 6 months	3%

Duloxetine may be used in patients with stress incontinence who don't respond to pelvic floor muscle exercises and decline surgical intervention

Important for me Less important

This patient is displaying typical symptoms of stress incontinence.

Guidelines recommend duloxetine as a second-line treatment if lifestyle measures (such as reducing caffeine and alcohol intake) and supervised pelvic floor muscle exercises are unsuccessful, and if the woman is not keen or suitable for surgical management.

It is thought to work by increasing serotonin and norepinephrine levels in the pudendal motor nucleus of the sacral spinal segments, thereby increasing urethral muscular tone and closure pressure.

It is not usually offered as first-line therapy as drug side-effects are common (affecting more than 10% of women) and it is less cost-effective than pelvic floor muscle training.

Ring pessaries are used as a non-surgical treatment option for pelvic organ prolapse.

Oxybutynin is an antimuscarinic drug which is used in treating urge incontinence. While some women have a mixed clinical picture, it is clear in the scenario that this woman only has stress incontinence.

Bladder training (also known as bladder drills) are recommended for urge incontinence. This method of behavioural therapy involves training the bladder to hold progressively larger volumes of urine by voiding at scheduled intervals.

Pelvic floor exercises, supervised by a continence adviser, specialist nurse or women's health physiotherapist, should be trialled for at least 3 months in order for maximum benefit. As this woman continues to have troublesome symptoms after 6 months of exercises, it would not be appropriate to advise her to simply continue the same strategy.

👍 👎 Discuss (4) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity

  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

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Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

Report broken link

Media

URINARY INCONTINENCE

Urinary incontinence

Osmosis - YouTube 👍 0 👎 1

Report broken media

Score: **24.3%**

1 ✓

PassMedicine

Question 269 of 414 ✗

A 45-year-old woman presents to the emergency department with abdominal pain. She describes a 24-hour history of right-sided loin pain, radiating to her groin. She mentions that this has happened multiple times in the past. Her past medical history is significant for Sjogren's syndrome, for which she takes artificial tears and artificial saliva.

Selected investigation results are shown below:

Venous blood gas:

pH	7.30	(7.35-7.45)
K^+	3.0 mmol/L	(3.5 - 5.0)
Bicarbonate	17 mmol/L	(22 - 29)

CT kidneys, ureter, bladder:	5mm non-obstructing calculus at the right vesicoureteric junction

What is the most likely unifying diagnosis?

Cryoglobulinaemia	2%
Type 1 renal tubular acidosis	77%
Type 2 renal tubular acidosis	15%
Type 3 renal tubular acidosis	3%
Type 4 renal tubular acidosis	4%

Type 1 renal tubular acidosis (distal) complication - renal stones

Important for me Less important

The correct answer is **type 1 renal tubular acidosis**. This patient has presented with recurrent renal colic. Her venous blood gas results show hypokalaemic metabolic acidosis. All of these features point towards a unifying diagnosis of type 1 (distal) renal tubular acidosis (RTA), where the intercalated cells of the distal tubules fail to secrete hydrogen ions and reabsorb potassium. The predisposition to renal stone formation is explained by hypercalciuria, together with the proclivity of calcium phosphate stones to form at high urinary pH. Type 1 RTA is associated with Sjogren's syndrome, which is an additional clue from this patient's past medical history.

Cryoglobulinaemia can be associated with Sjogren's syndrome. However, it is not classically associated with hypokalaemic metabolic acidosis or renal stone formation and is not the best answer here. It may present with a vasculitic rash or symptoms of hyperviscosity.

Type 2 renal tubular acidosis is incorrect. Although this can present as hypokalaemic metabolic acidosis, it is not associated with urolithiasis or Sjogren's syndrome as strongly as type 1 renal tubular acidosis.

Type 3 renal tubular acidosis is an extremely rare cause of hypokalaemic metabolic acidosis. As it is very uncommon, and not strongly associated with Sjogren's syndrome or urolithiasis, it is not the best option available.

Type 4 renal tubular acidosis is incorrect as this tends to cause hyperkalemic metabolic acidosis due to either hypoaldosteronism or resistance to aldosterone.

Discuss (5) Improve

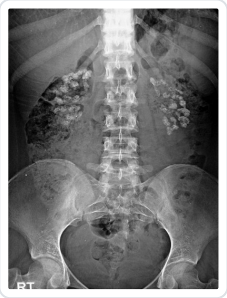
Next question

Renal tubular acidosis

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

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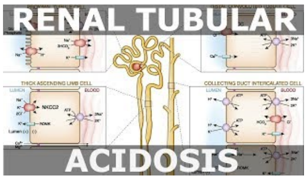

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← Question 270 of 414 ✗ →

Which one of the following statements regarding galactosaemia is **incorrect**?

Autosomal recessive inheritance	18%
May cause cataracts	10%
Caused by the absence of galactose-1-phosphate uridyl transferase	15%
🟥 May cause jaundice	21%
🟩 May cause peripheral neuropathy	37%

Discuss (5) Improve

Next question

Galactosaemia ★

Galactosaemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

Features
- jaundice
- failure to thrive
- hepatomegaly
- cataracts
- hypoglycaemia after exposure to galactose
- Fanconi syndrome

Diagnosis
- urine reducing substances

Management is with a galactose free diet

Next question

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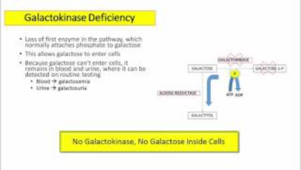

Galactokinase Deficiency

- Loss of first enzyme in the pathway, which normally attaches phosphate to galactose
- This allows galactose to enter cells
- Because galactose can't enter cells, it remains in blood and urine, where it can be detected on routine testing
  - Blood → galactosemia
  - Urine → galactosuria

No Galactokinase, No Galactose Inside Cells

GALACTOKINASE
GALACTOSE
GALACTOSE-1-P
ALDOSE REDUCTASE
ATP ADP
GALACTITOL

Galactose Metabolism

12DaysinMarch - YouTube 👍 17 👎 1

Report broken media

Score: **24.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗

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Question 271 of 414 ✗

A 20-year-old male, is referred to the endocrinology clinic due to concerns about delayed puberty and difficulty gaining muscle mass. On examination, he is taller than his peers, with minimal facial and body hair. He has gynaecomastia and small, firm testes are palpated. His intelligence and cognitive development are within the normal range. Blood tests reveal elevated levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH) but low levels of testosterone.

What is the most likely diagnosis ?

	Androgen insensitivity syndrome	5%
	Congenital adrenal hyperplasia	2%
🟥	Kallmann's syndrome	17%
🟩	Klinefelter syndrome	76%
	Prader willi syndrome	0%

Klinefelter's syndrome causes high LH and low testosterone

Important for me Less important

The clinical presentation of delayed puberty, tall stature, gynaecomastia, small testes, and elevated levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH) with low testosterone is highly suggestive of **Klinefelter syndrome** .

While **Kallmann's syndrome** is associated with delayed puberty, it also presents with anosmia, which is not mentioned in the case. Testosterone levels may be low, but LH and FSH levels may also be low.

Individuals with **androgen insensitivity syndrome** typically have a female phenotype and may present with gynaecomastia, undescended testes, and little or no axillary and pubic hair. Testosterone levels are usually within the normal range or slightly elevated.

Prader-Willi syndrome involves intellectual disability, hyperphagia leading to obesity, and hypogonadism, but it does not typically present with elevated LH and FSH levels.

Congenital adrenal hyperplasia , particularly classic CAH, can lead to early signs of virilisation, but the hormonal profile involves elevated androgens and adrenal dysfunction. It does not typically present with tall stature or elevated LH and FSH levels.

Discuss (2) | Improve

Next question

Klinefelter's syndrome ★

Klinefelter's syndrome is associated with karyotype 47, XXY.

Features
- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels but low testosterone

Diagnosis is by karyotype (chromosomal analysis).

Next question

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Question 272 of 414 ✗

One of your patients is diagnosed with having the metabolic syndrome. Which one of the following is associated with this condition?

	Endometriosis	4%
	Hypothyroidism	29%
	Asymptomatic rise in amylase levels	8%
🟥	Elevated albumin levels	5%
🟩	Raised uric acid levels	54%

The correct answer is **Raised uric acid levels**. Metabolic syndrome, also known as Syndrome X or Insulin Resistance Syndrome, is a cluster of conditions that occur together, increasing the risk of heart disease, stroke and type 2 diabetes. These conditions include increased blood pressure, high blood sugar levels, excess body fat around the waist and abnormal cholesterol or triglyceride levels. Raised uric acid levels are commonly seen in metabolic syndrome due to insulin resistance. Insulin resistance reduces the kidney's ability to excrete uric acid leading to hyperuricemia.

Endometriosis is not directly associated with metabolic syndrome. Endometriosis is a chronic gynaecological disorder where tissues similar to the lining of the uterus (endometrium) grow outside the uterus causing pain and sometimes infertility. Although some studies suggest that women with endometriosis may have a higher risk of developing metabolic disorders later in life, it is not a direct consequence or feature of metabolic syndrome.

Hypothyroidism, while it can cause weight gain and increase cholesterol levels which are components of metabolic syndrome, it is not typically associated with metabolic syndrome itself. Hypothyroidism refers to an underactive thyroid gland that produces insufficient amounts of thyroid hormones leading to a slowing down of metabolism.

An **Asymptomatic rise in amylase levels** does not typically occur in patients with metabolic syndrome. Elevated serum amylase can indicate pancreatic inflammation or mumps but it's not directly linked to metabolic syndrome.

Finally, **Elevated albumin levels** are also not associated with metabolic syndrome. Albumin is a protein made by the liver and has many roles including maintaining oncotic pressure and transporting various substances throughout the body. High albumin levels could be due to dehydration or severe infection but they do not correlate directly with metabolic syndrome.

👍 👎 Discuss (6) Improve

Next question

Metabolic syndrome ★

Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time. It is thought that the key pathophysiological factor is insulin resistance.

SIGN recommend using criteria similar to those from the American Heart Association. The similarity of the International Diabetes Federation criteria should be noted. For a diagnosis of metabolic syndrome at least 3 of the following should be identified:

- elevated waist circumference: men > 102 cm, women > 88 cm
- elevated triglycerides: > 1.7 mmol/L
- reduced HDL: < 1.03 mmol/L in males and < 1.29 mmol/L in females
- raised blood pressure: > 130/85 mmHg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

The International Diabetes Federation produced a consensus set of diagnostic criteria in 2005, which are now widely in use. These require the presence of central obesity (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors:

- raised triglycerides level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- reduced HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
- raised blood pressure: > 130/85 mm Hg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

In 1999 the World Health Organization produced diagnostic criteria which required the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

- blood pressure: > 140/90 mmHg
- dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)

- central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
- microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

Other associated features include:

- raised uric acid levels
- non-alcoholic fatty liver disease
- polycystic ovarian syndrome

Next question

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Patient.info 👍 4 👎 1

Metabolic syndrome

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Score: **23.9%**

1 ✓

2 ✓

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← Question 273 of 414 ✗ →

You are called to the orthopaedic ward to review a 78-year-old man. The nurses have recorded his blood sugar level at 2.4mmol/L. He is recovering following surgery for a neck femur fracture. He has a history of hypertension, diabetes, and chronic renal failure.

On examination, he is slightly agitated but able to answer your questions, his heart rate is 78bpm and blood pressure 134/82mmHg.

What is the most appropriate first-line treatment?

	10% dextrose IV	10%
🟥	20% dextrose IV	18%
	Glucagon, IM	11%
🟩	Glucogel, orally	56%
	Sandwich, orally	5%

Hypoglycaemia treatment - if the patient is conscious and able to swallow the first-line treatment is a fast-acting carbohydrate by mouth i.e.. glucose liquids, tablets or gels

Important for me Less important

This patient is conscious and able to swallow so the most appropriate first-line treatment is a fast-acting oral carbohydrate. This can be as a liquid, tablet or gel, so in this case **glucogel** is the single best answer.

Intravenous 20% glucose solution may be given through a large vein to patients who are unconscious. In this case, the patient is drowsy but able to speak and so oral treatment would be the best first-line treatment. **10% dextrose IV** is not the recommended level to correct hypoglycaemia.

If the patient is unconscious or unable to swallow, **subcutaneous or intramuscular injection glucagon** may be given. In this case, the patient is conscious and so this is not the right answer.

A sandwich can be a useful adjunct after acutely treating the hypoglycaemic episode, but it is a slower acting carbohydrate than a fast-acting glucose liquid required in this scenario. In the acute phase, if the patient is alert, a quick-acting carbohydrate should be given.

👍 👎 Discuss (3) Improve

Next question

Hypoglycaemia ★

Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
  - causes exaggerated insulin secretion
  - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia

- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
  - Sweating
  - Shaking
  - Hunger
  - Anxiety
  - Nausea

- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
    - Weakness
    - Vision changes
    - Confusion
    - Dizziness
- Severe and uncommon features of hypoglycaemia include:
    - Convulsion
    - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):
    - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
    - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
    - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
    - If the patient is alert, a quick-acting carbohydrate may be given (as above)
    - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
    - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

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Postgraduate Medical Journal

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Question 274 of 414 ✗

A 29-year-female, who is 4 months post-partum, presents with a 3-week history of weight loss, heat intolerance, tremor, palpitation and diarrhoea. Pregnancy and birth were uncomplicated. On further questioning, she admits having taken off-license weight loss medication bought from the internet 1 month ago. Past medical history and family history are insignificant. She does not smoke or drink alcohol.

On physical examination, she has exophthalmos, brisk reflexes and fine tremor. Her vital signs were heart rate 98/minute, blood pressure 136/76 mmHg, temperature 36.5°C. The thyroid gland was diffusely enlarged.

Thyroid Stimulating Hormone (TSH)	0.02 mU/l
Free thyroxine (T4)	24 pmol/l
Total thyroxine (T4)	150 nmol/l

What is the most likely diagnosis?

	Exogenous thyroxine	28%
🟩	Graves' Disease	46%
🟥	Hashimoto's thyroiditis	2%
	Post-partum thyroiditis	22%
	De Quervain's thyroiditis	3%

Graves' disease may present first or become worse during the post-natal period

Important for me Less important

This is a case of hyperthyroidism due to Graves' disease. Graves' disease may manifest itself or worsen during pregnancy and the post-natal period.

Exophthalmos is a specific sign seen in Graves' disease and not in other hyperthyroid conditions.

Hashimoto's thyroiditis leads to hypothyroidism.

In post-partum thyroiditis, the woman initially develops hyperthyroidism immediately after birth followed by normal or sometimes decreased thyroid levels.

De Quervain's thyroiditis can present with pain and dysphagia and may lead to high, normal or low thyroid levels.

👍 👎 Discuss (9) Improve

Next question

Pregnancy: thyroid problems ★

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

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Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

Score: **23.7%**

1 ✓
2 ✓
3 ✓

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Question 275 of 414 ✗

A 45-year-old man is reviewed by his GP. He was recently diagnosed with type-2 diabetes mellitus and was started on modified-release metformin. He began to suffer from intolerable diarrhea, so it was discontinued.

On review today, his most recent HbA1c is 63.

What is the next most appropriate step in management?

	No treatment required	3%
🟩	Start gliclazide	61%
🟥	Start liraglutide	7%
	Start twice daily insulin regimen	4%
	Switch to standard-release formulation of metformin	25%

T2DM initial therapy: if metformin is contraindicated (and no risk of CVD, established CVD or chronic heart failure) → choice of DPP-4 inhibitor or Pioglitazone or Sulfonylurea or even SGLT-2 (if NICE criteria met)

Important for me Less important

Start gliclazide is correct. Metformin was not tolerated in this patient, therefore the next option should be either a DPP4 inhibitor, SGLT2 inhibitor, sulfonylurea, or thiazolidinedione. Of the available answers, only gliclazide (a sulfonylurea) is a suitable next agent.

No treatment required is incorrect. This patient has a diagnosis of type 2 diabetes and his HBA1C remains raised, he therefore requires treatment.

Start liraglutide is incorrect. Liraglutide is a GLP-1 analog. These are used if triple therapy in type 2 diabetes is unsuccessful and the patient's BMI is >35 or if insulin is not acceptable.

Start twice daily insulin regimen is incorrect. Insulin is used if triple therapy in type 2 diabetes is unsuccessful. This patient should first be tried on a combination of up to three of a DPP4 inhibitor, SGLT2 inhibitor, sulfonylurea, or thiazolidinedione.

Switch to standard-release formulation of metformin is incorrect. If a patient taking a standard-release formulation of metformin develops gastrointestinal side effects, these can sometimes be relieved by switching to a modified-release preparation, but not the other way around. This answer is therefore incorrect.

Discuss Improve

Next question

Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015
- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly

- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

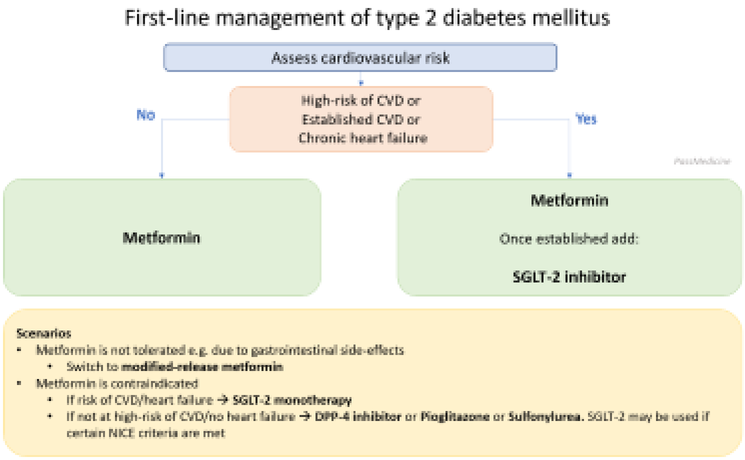
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios
- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

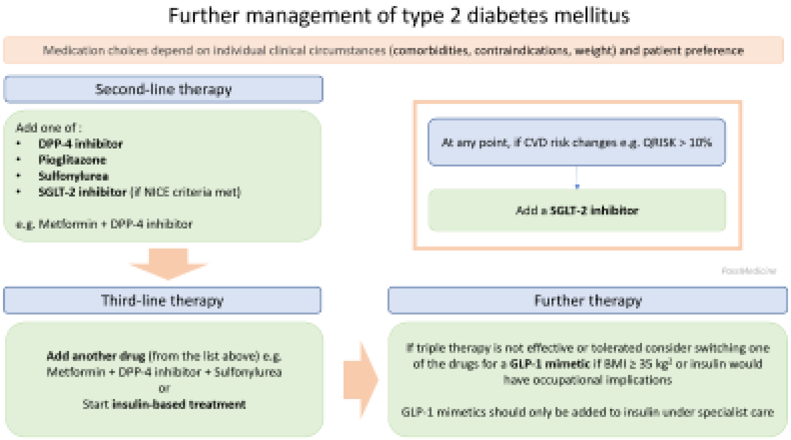
Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.
- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated
- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances **(comorbidities, contraindications, weight) and patient preference**
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a **SGLT-2 inhibitor**
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea or Start **insulin-based treatment**
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a **GLP-1 mimetic** if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

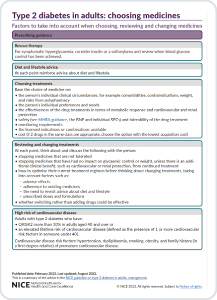
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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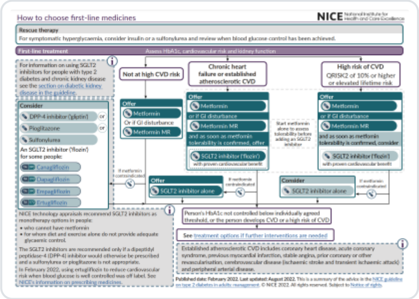

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR

Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated
Offer
SGLT2 inhibitor alone
If metformin contraindicated

Consider
SGLT2 inhibitor alone
If metformin contraindicated

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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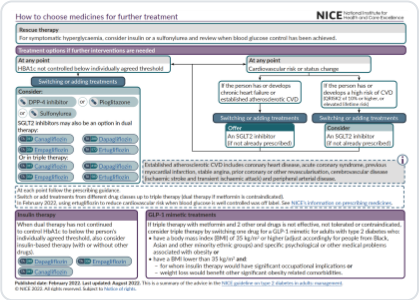

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments
Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin
Or in triple therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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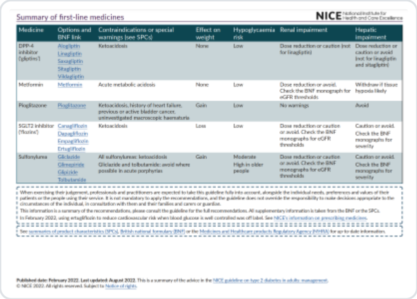

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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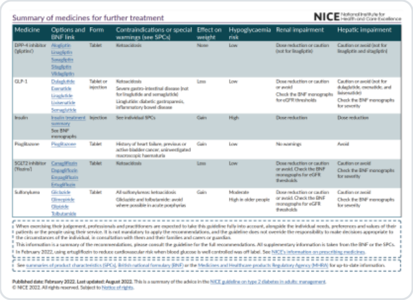

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

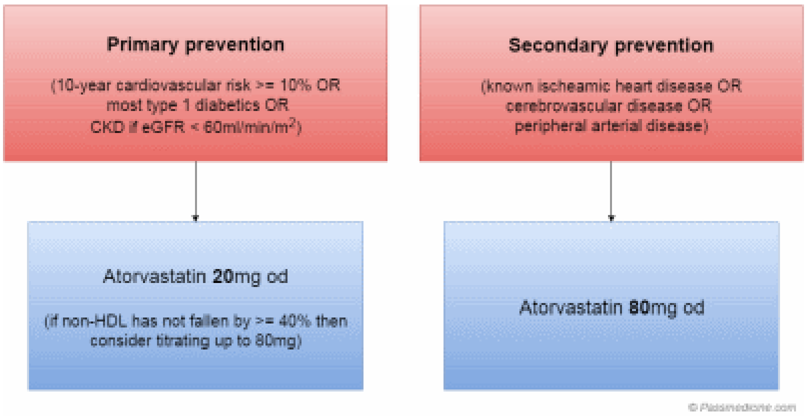
	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

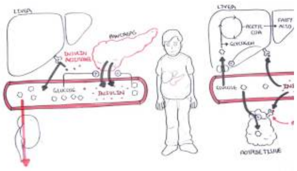
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media

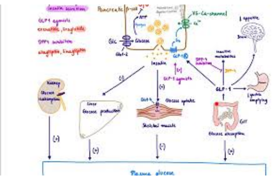


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

Report broken media

Score: **23.6%**

1 ✓
2 ✓
3 ✓

PassMedicine

Question 276 of 414 ✗

A 33-year-old woman is seen in the infertility clinic with her partner.

Her past medical history includes polycystic ovarian syndrome. Her BMI is 27kg/m^2.

They have been trying to conceive for over 2 years without success.

Preliminary investigations have already shown there are no problems with her partner's fertility.

What is the most appropriate first-line management?

	Bromocriptine	2%
🟩	Clomifene	69%
	Gonadotrophins	2%
	Intrauterine insemination	2%
🟥	Metformin	26%

Infertility in PCOS - clomifene is typically used first-line

Important for me Less important

Clomifene is correct. Clomifene is used in polycystic ovarian syndrome to induce ovulation. Clomifene is an anti-oestrogen that blocks oestrogen receptors in the hypothalamus. This reduces the negative feedback of oestrogen and causes a resultant increase in gonadotropin release.

Bromocriptine is incorrect. Bromocriptine is a dopamine agonist, and the resultant increase in dopaminergic activity inhibits prolactin release from the pituitary gland. It can be used to treat infertility if the infertility is due to hyperprolactinaemia.

Gonadotrophins is incorrect. These would only be used if initial treatment with clomifene has failed.

Intrauterine insemination is incorrect. This would also be reserved for the most resistant cases of infertility due to polycystic ovarian syndrome and would not be used first-line.

Metformin is incorrect. Metformin is also used in patients with polycystic ovarian syndrome to improve infertility, however, clomifene has shown to be superior to metformin in this regard. It may be used in combination with clomifene if the patient is obese. Although this patient is overweight, she is not obese.

👍 👎 💬 Discuss (3) Improve

Next question

Polycystic ovarian syndrome: management ★

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

General

- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne

- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility

- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and

concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

Next question

Textbooks

High-yield textbook

Extended textbook

Links

RCOG 👍 4 👎 0

Opinion paper on metformin in PCOS

ESHRE (European Society of Human Reproduction and Embryology) 👍 1 👎 0

2018 International Evidence Based Guideline for the Assessment and Management of PCOS

Patient.info 👍 1 👎 0

Polycystic ovarian syndrome review

Clinical Knowledge Summaries 👍 3 👎 1

Polycystic ovarian syndrome

Royal College of Obstetricians and Gynaecologists 👍 2 👎 1

2014 Long-term Consequences of Polycystic Ovary Syndrome

NEJM 👍 1 👎 1

Summary of recent trial comparing metformin to clomifene

Report broken link

Score: **23.6%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗
16	✗
17	✓
18	✗
19	✗
20	✓
21	✓

PassMedicine

Question 277 of 414 ✗

A 64-year-old patient is prescribed pegvisomant for the treatment of acromegaly. What is the mechanism of action of pegvisomant?

	IGF-1 receptor antagonist	24%
🟩	Growth hormone receptor antagonist	53%
	IGF-1 receptor agonist	5%
🟥	Growth hormone receptor agonist	4%
	Long-acting somatostatin analogue	14%

The correct answer is **Growth hormone receptor antagonist**. Pegvisomant works by blocking the effects of excess growth hormone in the body. It does this by binding to the growth hormone receptors on cells and preventing the natural hormone from attaching. This effectively reduces the symptoms of acromegaly, a condition characterised by the overproduction of growth hormone usually due to a pituitary adenoma.

The first option, **IGF-1 receptor antagonist**, is incorrect because pegvisomant does not act on IGF-1 (Insulin-like Growth Factor-1) receptors. IGF-1 is a hormone produced in the liver and other tissues in response to growth hormone and it mediates many of the growth-promoting effects. While reducing IGF-1 levels can be beneficial in treating acromegaly, pegvisomant achieves this indirectly through the antagonism of growth hormone receptors, not by blocking IGF-1 receptors.

The third option, **IGF-1 receptor agonist**, is also incorrect for similar reasons. Pegvisomant does not stimulate IGF-1 receptors; instead, it blocks growth hormone receptors which leads to decreased production of IGF-1.

Growth hormone receptor agonist is another incorrect option. An agonist would enhance or mimic the action of growth hormones, which would exacerbate acromegaly rather than treat it. On the contrary, pegvisomant acts as an antagonist at these receptors thereby reducing their activity.

Finally, pegvisomant is not a **long-acting somatostatin analogue**. Somatostatin analogues like octreotide or lanreotide are a different class of drugs used in acromegaly treatment - they inhibit the release of growth hormone from the pituitary gland but do not block its action at target cells as pegvisomant does.

In summary, while all options relate to pathways involved in growth regulation and could theoretically have an impact on conditions like acromegaly, only one - 'growth hormone receptor antagonist' - accurately describes how pegvisomant functions therapeutically.

Discuss (1) Improve

Next question

Acromegaly: management

Trans-sphenoidal surgery is the first-line treatment for acromegaly in the majority of patients.

If a pituitary tumour is inoperable or surgery unsuccessful then medication may be indicated:

- somatostatin analogue
    - directly inhibits the release of growth hormone
    - for example octreotide
    - effective in 50-70% of patients
- pegvisomant
    - GH receptor antagonist - prevents dimerization of the GH receptor
    - once daily s/c administration
    - very effective - decreases IGF-1 levels in 90% of patients to normal
    - doesn't reduce tumour volume therefore surgery still needed if mass effect
- dopamine agonists
    - for example bromocriptine
    - the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
    - effective only in a minority of patients

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

Next question

Textbooks

High-yield textbook

Extended textbook

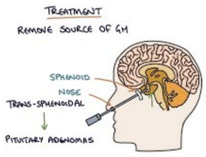
Links

Postgraduate Medical Journal 👍 7 👎 2

Modern treatment of acromegaly

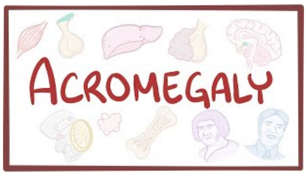
Report broken link

Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 16 👎 3


ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 8 👎 2

Report broken media

Score: **23.5%**

1 ✓
2 ✓

PassMedicine

Question 278 of 414 ✕

A 54-year-old man with type 2 diabetes mellitus is started on exenatide. Which one of the following statements regarding exenatide is **incorrect**?

	Typically results in weight loss	9%
	May be combined with a sulfonylurea	23%
🟩	The major adverse effect is flu-like symptoms	52%
🟥	May be combined with metformin	4%
	Must be given by subcutaneous injection	12%

Exenatide causes vomiting

Important for me Less important

The correct answer is '**The major adverse effect is flu-like symptoms**'. Exenatide, a glucagon-like peptide-1 receptor agonist (GLP-1), is used in the management of type 2 diabetes. The most common side effects of exenatide are gastrointestinal disturbances such as nausea, vomiting and diarrhoea. Although some patients may experience flu-like symptoms, these are not considered the major adverse effect of this medication.

Now let's discuss each of the incorrect options:

'**Typically results in weight loss**' is true. This is one of the beneficial effects of exenatide and other GLP-1 receptor agonists. They slow gastric emptying, increase satiety and therefore can result in weight loss which is often desirable in patients with type 2 diabetes who are frequently overweight or obese.

'**May be combined with a sulfonylurea**' is also true. According to NICE guidelines, GLP-1 mimetics like exenatide can be used as a dual therapy regimen with metformin or a sulfonylurea if metformin is contraindicated or not tolerated.

'**May be combined with metformin**' is another correct statement. As mentioned earlier, exenatide can be used in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.

Lastly, '**Must be given by subcutaneous injection**' is a correct statement as well. Exenatide does not come in an oral form due to its peptide nature which would lead it to being digested in the stomach. Therefore it must be administered via subcutaneous injection.

👍 👎 Discuss (6) Improve

Next question

Diabetes mellitus: GLP-1 drugs

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points
- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

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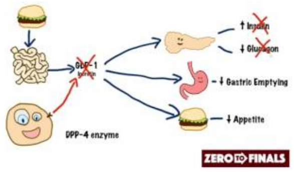
Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

Report broken link

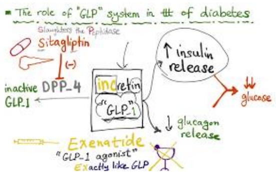
Media



GLP-1
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

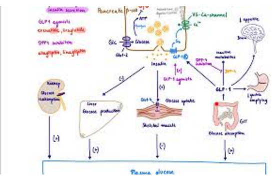
Zero to Finals - YouTube 👍 45 👎 2



The role of "GLP" system in tt of diabetes
Sitagliptin
(-)
inactive GLP-1
DPP-4
incretin
"GLP"
↑ insulin release
↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



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← Question 279 of 414 ✗ ⚐ →

A 3-year-old boy is investigated for lethargy. Examination is unremarkable with a blood pressure of 90/46 mmHg (normal for his age). Blood tests reveal:

Na^+	140 mmol/l
K^+	2.6 mmol/l
Bicarbonate	33 mmol/l
Urea	4.2 mmol/l
Creatinine	91 µmol/l

Which one of the following conditions is most likely to be responsible?

	Cushing's syndrome	5%
🟥	Conn's syndrome	10%
	11-beta hydroxylase deficiency	11%
🟩	Bartter's syndrome	64%
	Liddle's syndrome	11%

Bartter's syndrome is associated with normotension

Important for me Less important

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na^+ K^+ 2Cl- cotransporter in the ascending loop of Henle

Discuss (10) Improve

Next question

Hypokalaemia and hypertension ★

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not

Hypokalaemia with hypertension

- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
- 11-beta hydroxylase deficiency*

Carbenoxolone, an anti-ulcer drug, and liquorice excess can potentially cause hypokalaemia associated with hypertension

Hypokalaemia without hypertension

- diuretics
- GI loss (e.g. Diarrhoea, vomiting)
- renal tubular acidosis (type 1 and 2**)
- Bartter's syndrome
- Gitelman syndrome

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**type 4 renal tubular acidosis is associated with hyperkalaemia

Next question

Textbooks

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PassMedicine

Question 280 of 414 ✗

Which one of the following regarding the management of thyroid problems during pregnancy is **incorrect**?

	Maternal free thyroxine levels should be kept in the upper third of the normal reference range when treating thyrotoxicosis	12%
	Increased levels of thyroxine-binding globulin are seen in pregnancy	7%
🟩	Block-and-replace is preferable in pregnancy compared to antithyroid drug titration	71%
🟥	Breast feeding is safe whilst on thyroxine	5%
	Untreated thyrotoxicosis increases the risk of premature labour	4%

The correct answer is '**Block-and-replace is preferable in pregnancy compared to antithyroid drug titration**'. This statement is incorrect as per the UK guidelines. The block-and-replace regimen, which involves giving high-dose antithyroid medication along with levothyroxine replacement, is not recommended during pregnancy due to the risk of fetal hypothyroidism and goitre. Instead, the titration regimen, where a low dose of antithyroid medication is used to control hyperthyroidism, is preferred.

Discussing the other options:

'**Maternal free thyroxine levels should be kept in the upper third of the normal reference range when treating thyrotoxicosis**' - this statement is correct. It's important to avoid overtreatment leading to iatrogenic hypothyroidism while managing thyrotoxicosis during pregnancy. Hence, free thyroxine levels are targeted towards the upper third of the normal reference range.

'**Increased levels of thyroxine-binding globulin are seen in pregnancy**' - this statement is also accurate. During pregnancy, there's an increase in estrogen levels which stimulates hepatic production of thyroxine-binding globulin (TBG), thus increasing its serum concentration.

'**Breast feeding is safe whilst on thyroxine**' - this option is true as well. Levothyroxine (synthetic T4) used for the treatment of hypothyroidism does not significantly pass into breast milk and hence doesn't pose a risk for breastfeeding infants.

Finally, '**Untreated thyrotoxicosis increases the risk of premature labour**' - this statement holds true too. If left untreated or poorly controlled, hyperthyroidism can lead to several adverse maternal and fetal outcomes including preterm labour, preeclampsia and intrauterine growth restriction among others.

👍 👎 Discuss (6) Improve

Next question

Pregnancy: thyroid problems ★

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

Score: **23.2%**

1 ✓
2 ✓
3 ✓
4 ✗

PassMedicine

← Question 281 of 414 ✗ ⚐ →

A 55-year-old taxi driver with type 2 diabetes mellitus comes for review. When he was diagnosed 12 months ago he was started on metformin and the dose was titrated up. His IFCC-HbA1c one year ago was 75 mmol/mol (DCCT-HbA1c 9%) and is now 69 mmol/mol (8.5%). His body mass index is 33 kg/m². What is the most appropriate next step in management?

	Add exenatide	21%
🟩	Add sitagliptin	61%
	Add glipizide	11%
🟥	Make no changes to his medication	4%
	Add insulin	4%

His HbA1c is still significantly above target so some change to the medication is indicated.

The NICE type 2 diabetes mellitus guidelines would *generally* advocate the use of a sulfonylurea in this situation.

However. the patient is a taxi driver and overweight. A DPP-4 inhibitor such as sitagliptin would be ideal in this situation. There is no risk of hypoglycaemia and they DPP-4 inhibitors are weight neutral.

👍 👎 Discuss (9) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle +	53 mmol/mol

Management of T2DM	HbA1c target
sulfonylurea)	(7.0%)

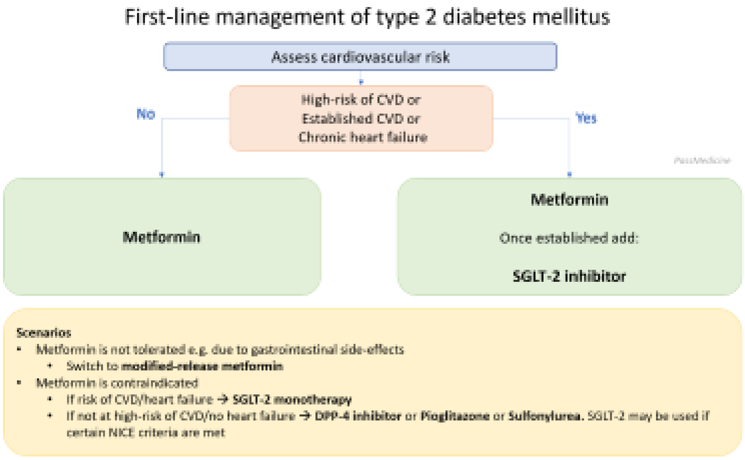
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or
Established CVD or
Chronic heart failure
No
Yes
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios

- Metformin is not tolerated e.g. due to gastrointestinal side-effects
    - Switch to **modified-release metformin**
- Metformin is contraindicated
    - If risk of CVD/heart failure → **SGLT-2 monotherapy**
    - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors

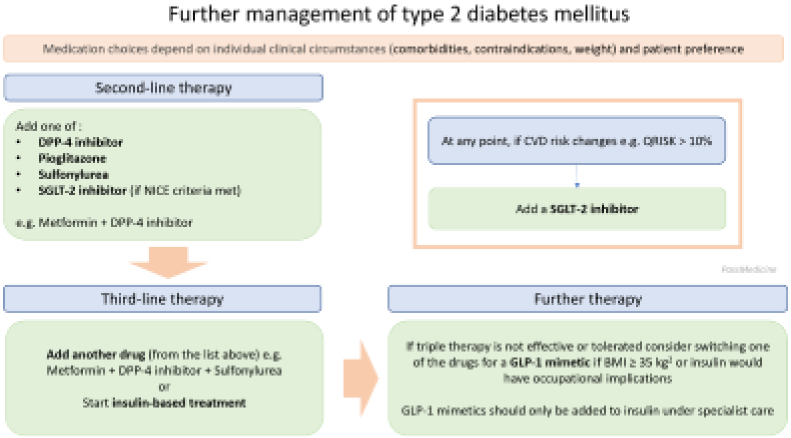
- should also be given in addition to metformin if any of the following apply:
    - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)

  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m² and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

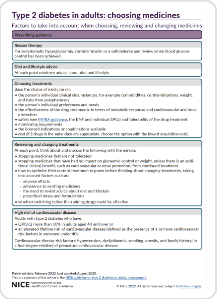
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

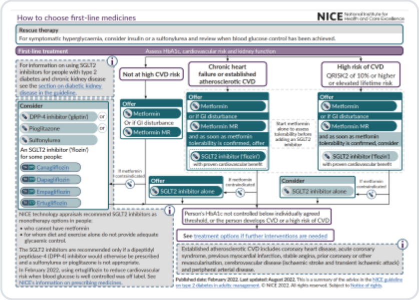
Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

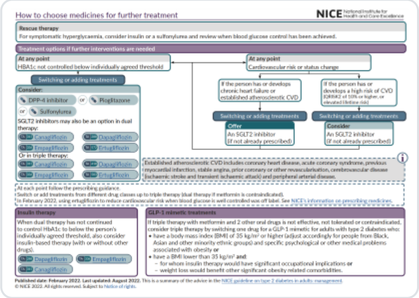


Type 2 diabetes in adults: choosing medicines

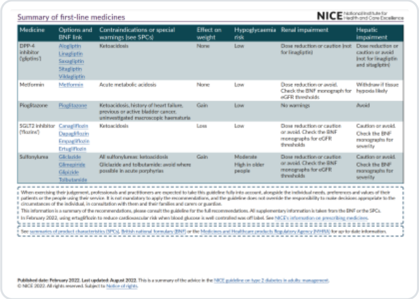
Factors to take into account when choosing, reviewing and changing medicines



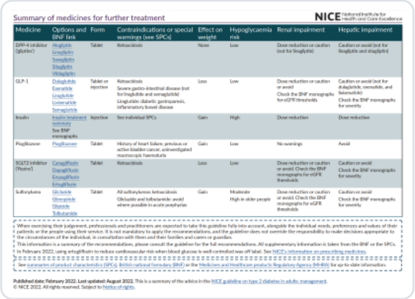
How to choose first-line medicines



How to choose medicines for further treatment



Summary of first-line medicines



Summary of medicines for further treatment

Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

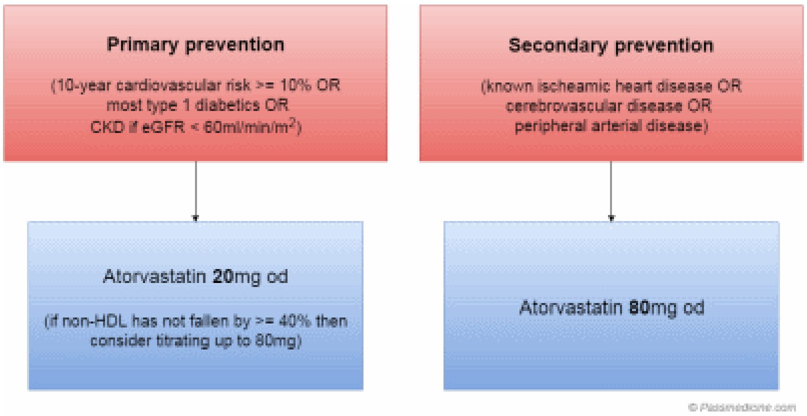
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR
most type 1 diabetics OR
CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR
cerebrovascular disease OR
peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then
consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

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Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

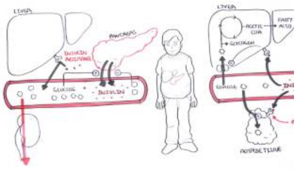
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3

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Question 282 of 414

A 53-year-old man presents with abnormal enlargement of both breasts which has gradually progressed over several months. The patient has several medical conditions including HIV, depression, heart failure and gastritis.

Hormonal testing confirms an increased oestrogen: androgen ratio and in the absence of another clear cause, the likely diagnosis is thought to be secondary to one of his medications.

What medication is likely to have caused the patient's presentation?

Amitriptyline	7%
Digoxin	69%
Emtricitabine/tenofovir (Truvada)	11%
Furosemide	5%
Ranitidine	8%

Digoxin can cause drug-induced gynaecomastia

Important for me Less important

This patient has presented with the non-cancerous, abnormal enlargement of one or both breasts in a male known as gynaecomastia. Gynaecomastia results from a hormone imbalance with there being multiple conditions that can cause this including chronic disease, hypogonadism and refeeding syndrome. However, a significant proportion of cases are a result of a medication side effect. Several drugs can cause gynaecomastia but one of the most common causes is **digoxin**. Due to the similarity between the structure of digoxin and oestrogen, the drug is believed to act direct at oestrogen receptors, resulting in the hormone imbalance responsible for gynaecomastia.

Antipsychotic such as risperidone are known to cause gynaecomastia because of their dopamine-blocking action, increasing prolactin levels. **Amitriptyline** however does not affect prolactin levels or therefore hormone balance.

Gynaecomastia has been associated in some cases with anti-retroviral therapy (ART), typically efavirenz, although the mechanism is not fully understood. **Emtricitabine/tenofovir (Truvada)** has not been associated with gynaecomastia and patients who develop the side effect have displayed a resolution of the abnormal growth when placed on alternative ART regimes including Truvada.

The commonly used diuretic spironolactone has been associated with gynaecomastia due to several mechanisms including an increase in testosterone production and peripheral conversion of testosterone to oestradiol. **Furosemide** does not cause these same side effects and therefore has not been associated with gynaecomastia.

Protein pump inhibitors (PPIs) have been observed to inhibit specific liver enzymes responsible for metabolising oestradiol, therefore increasing oestradiol levels and causing a hormone imbalance. As such gynaecomastia is a recognised side effect of PPIs however the same effect is not seen in histamine receptor antagonists such as **ranitidine**.

👍 | 👎 | 💬 Discuss (2) | Improve

Next question

Gynaecomastia ★

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia
- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia
- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis

- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

Next question

Textbooks

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Extended textbook

Score: **23%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗

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Question 283 of 414 ✓

You review a 68-year-old man who has chronic obstructive pulmonary disease (COPD). Each year he typically has around 7-8 courses of oral prednisolone to treat infective exacerbations of his COPD. Which one of the following adverse effects is linked to long-term steroid use?

Osteomalacia	19%
Enophthalmos	1%
Leucopaenia	7%
Avascular necrosis	73%
Constipation	1%

The correct answer is **Avascular necrosis**. This condition refers to the death of bone tissue due to a lack of blood supply, which can lead to tiny breaks in the bone and the bone's eventual collapse. Avascular necrosis is a well-documented complication of long-term corticosteroid use, such as prednisolone. Steroids are thought to interfere with the ability of blood to flow to the bones.

Osteomalacia is not typically associated with steroid use. Osteomalacia refers to softening of the bones, usually caused by severe vitamin D deficiency. While steroids can affect bone health, they do so by increasing bone resorption and decreasing new bone formation leading to osteoporosis rather than osteomalacia.

Enophthalmos, or the sinking back of one or both eyeballs into the orbits, is also not linked to steroid use. It is more commonly seen in conditions such as Horner's syndrome or following trauma or surgery.

Leucopaenia, a decrease in the number of white blood cells (leukocytes) in the blood, is generally not associated with long-term steroid use either. On the contrary, corticosteroids like prednisolone typically cause leukocytosis (an increase in white blood cell count) due to its demargination effect.

Finally, **Constipation** is not a common side effect of long-term oral corticosteroid use. More common gastrointestinal side effects include dyspepsia and peptic ulcer disease.

Discuss Improve

Next question

Corticosteroids ★

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	**Glucocorticoid activity, high mineralocorticoid activity,**	**Predominant glucocorticoid activity, low mineralocorticoid activity**	**Very high glucocorticoid activity, minimal mineralocorticoid activity**
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

The side effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects

- endocrine
  - impaired glucose regulation
  - increased appetite/weight gain
  - hirsutism
  - hyperlipidaemia
- Cushing's syndrome
  - moon face
  - buffalo hump
  - striae
- musculoskeletal
  - osteoporosis
  - proximal myopathy

    - avascular necrosis of the femoral head
- immunosuppression
    - increased susceptibility to severe infection
    - reactivation of tuberculosis
- psychiatric
    - insomnia
    - mania
    - depression
    - psychosis
- gastrointestinal
    - peptic ulceration
    - acute pancreatitis
- ophthalmic
    - glaucoma
    - cataracts
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects
- fluid retention
- hypertension

Selected points on the use of corticosteroids:
- patients on long-term steroids should have their doses doubled during intercurrent illness
- longer-term systemic corticosteroids suppress the natural production of endogenous steroids. They should therefore not be withdrawn abruptly, as this may precipitate an Addisonian crisis
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have:
    - received more than 40mg prednisolone daily for more than one week
    - received more than 3 weeks of treatment
    - recently received repeated courses

Next question

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← Question 284 of 414 ✓ →

A 56-year-old man presents to his GP with an increasing amount of breast tissue.

He was discharged from the hospital 2-months ago. Whilst an inpatient, he was started on a new medication for atrial fibrillation.

What medication is the likely cause of his new symptom?

Amiodarone	14%
Apixaban	1%
Bendroflumethiazide	7%
Bisoprolol	3%
Digoxin	74%

Digoxin can cause drug-induced gynaecomastia

Important for me Less important

Digoxin can cause gynaecomastia.

Amiodarone has multiple side effects including thyroid dysfunction, lung fibrosis, photosensitivity and hepatotoxicity. It does not cause gynaecomastia.

Apixaban can cause bleeding. It does not cause gynaecomastia.

Bendroflumethiazide does not cause gynaecomastia. Spironolactone, an aldosterone-antagonist, is the most common drug cause of gynaecomastia.

Bisoprolol can cause symptomatic bradycardia. It does not cause gynaecomastia.

Discuss (1) Improve

Next question

Gynaecomastia

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia
- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

Drug causes of gynaecomastia
- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia
- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

Next question

PassMedicine

Question 285 of 414 ✕

A 45-year-old man is reviewed in the diabetes clinic. The following results are obtained:

Urinalysis	NAD
HbA1c	69 mmol/mol

Gliclazide is added to the metformin he already takes. What is the minimum time period after which the HbA1c should be repeated?

	6 months	7%
	1 month	4%
	2 weeks	3%
🟩	3 months	83%
🟥	4 months	3%

A more accurate answer would probably be 2 months but this is not given as an option. See the explanation below

Discuss (6) Improve

Next question

Glycosylated haemoglobin

Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus. HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration. The level of HbA1c therefore is dependent on:

- red blood cell lifespan
- average blood glucose concentration

A number of conditions can interfere with accurate HbA1c interpretation:

Lower-than-expected levels of HbA1c (due to reduced red blood cell lifespan)	**Higher-than-expected levels of HbA1c (due to increased red blood cell lifespan)**
Sickle-cell anaemia GP6D deficiency Hereditary spherocytosis Haemodialysis	Vitamin B12/folic acid deficiency Iron-deficiency anaemia Splenectomy

HbA1c is generally thought to reflect the blood glucose over the previous '3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks. NICE recommend '*HbA1c should be checked every 3-6 months until stable, then 6 monthly*'.

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

HBA1c (%)	**Average plasma glucose (mmol/l)**	**IFCC-HbA1c (mmol/mol)**
5	5.5	
6	7.5	42
7	9.5	53
8	11.5	64
9	13.5	75
10	15.5	
11	17.5	
12	19.5	

From the above we can see that average plasma glucose = (2 * HbA1c) - 4.5

Next question

PassMedicine

Question 286 of 414 ✗

A 33-year-old woman is referred to the endocrinology clinic with thyrotoxicosis. Recent blood tests show the following:

TSH	< 0.05 mu/l
Free T4	25 pmol/l
Anti-thyroid peroxidase antibodies	115 IU/mL (< 35 IU/mL)

A smooth, non-tender goitre is noted on examination the neck. The patient also has exophthalmos although there is no ophthalmoplegia, no reduction in visual acuity and no eye symptoms present.

What is the most appropriate management?

	Radioiodine treatment	15%
🟩	Carbimazole	66%
	Propranolol	7%
🟥	Fine needle aspiration biopsy of the thyroid gland	4%
	Intravenous corticosteroids	7%

This patient has Graves' disease as evidenced by the thyrotoxicosis, goitre, thyroid eye disease and anti-thyroid peroxidase antibodies.

Radioiodine treatment should be avoided given the presence of thyroid eye disease so carbimazole is a better treatment option.

If her eye disease was severe then an ophthalmologist should be consulted. Options for severe thyroid eye disease include systemic steroids and radiotherapy.

Discuss (6) Improve

Next question

Graves' disease: management ★

Despite many trials, there is no clear guidance on the optimal management of Graves' disease. Treatment options include anti-thyroid drugs (ATDs, for example carbimazole), radioiodine treatment and surgery.

Anti-thyroid drugs have emerged as the most popular first-line therapy for Graves' disease in recent years. Factors that particularly support their use include anti-thyroid drugs significant symptoms of thyrotoxicosis, or patients with a significant risk of hyperthyroid complications (e.g. elderly patients, cardiovascular disease).

Initial treatment to control symptoms

- propranolol is used to help block the adrenergic effects

NICE Clinical Knowledge Summaries recommended that patients with Graves' disease are referred to secondary care for ongoing treatment.

- NICE suggest carbimazole should be considered in primary care if patients symptoms are not controlled with propanolol

ATD therapy

- carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- the major complication of carbimazole therapy is agranulocytosis
- an alternative regime is termed 'block-and-replace'
    - carbimazole is started at 40mg
    - thyroxine is added when the patient is euthyroid
    - treatment typically lasts for 6-9 months
    - patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime

Radioiodine treatment

- often used in patients who relapse following ATD therapy or are resistant to primary ATD treatment
- contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years. Thyroid eye disease is a relative contraindication, as it may worsen the condition
- the proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

Question 287 of 414 ✓

A 53-year-old man is reviewed in primary care for an annual diabetes check-up. Last year, he was started on maximum-dose metformin after failing to reduce his HbA1c through dietary changes alone. His HbA1c on this occasion has come back at 60 mmol/L. He follows a very low carbohydrate diet and has a past medical history of inflammatory bowel disease, non-alcoholic fatty liver disease, and stage IV chronic kidney disease. For work, he drives a lorry, so he does not want to take medications that risk hypoglycaemia.

What is the most appropriate treatment?

Dapagliflozin	27%
Exenatide	8%
Gliclazide	5%
Linagliptin	51%
Pioglitazone	9%

T2DM on metformin, if HbA1c has risen to 58 mmol/mol then one of the following should be offered depending on the individual clinical scenario:

- DPP-4 inhibitor
- pioglitazone
- sulfonylurea
- SGLT-2 inhibitor (if NICE criteria met)

Important for me Less important

Linagliptin is the correct answer. This patient requires escalation of his oral medications since his HbA1c is greater than 58 mmol/L, despite treatment with metformin. The most appropriate agent is linagliptin, which is a DPP-4 inhibitor. This is the most appropriate choice as the dose does not need to be adjusted in chronic renal impairment, is not associated with hypoglycaemia, and can be given alongside low carbohydrate diets.

Dapagliflozin is incorrect. Generally, SGLT2 inhibitors should not be given to patients with moderate-to-severe renal impairment. They should also be avoided in patients who consume very low amounts of carbohydrates.

Exenatide is incorrect. Exenatide is a GLP-1 agonist. It should be used with caution in patients with renal and hepatic impairment and, therefore, would not be a good choice for this patient.

Gliclazide is incorrect. Gliclazide is a sulfonylurea that is associated with hypoglycaemia. Given his job as a lorry driver, this would not be the best therapeutic decision.

Pioglitazone is incorrect. Glitazone medications should be avoided in patients with hepatic impairment. It also risks bladder cancer and heart failure, two important considerations in a relatively young patient.

Discuss (8) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

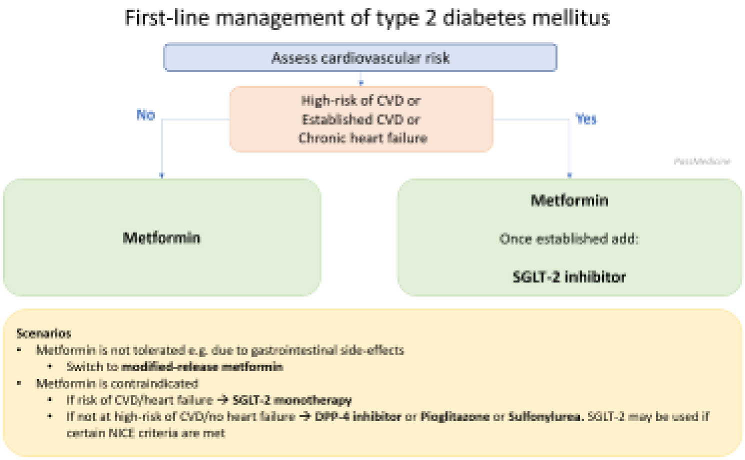
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or
Established CVD or
Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios

- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

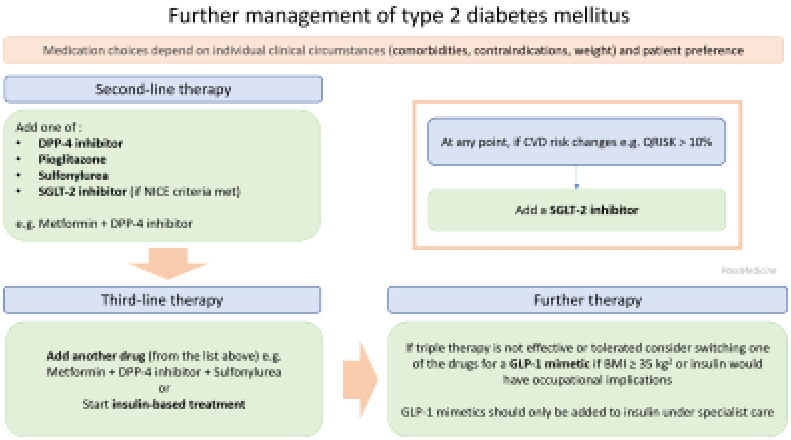
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care
PassMedicine

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

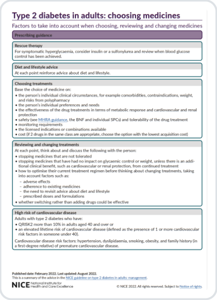
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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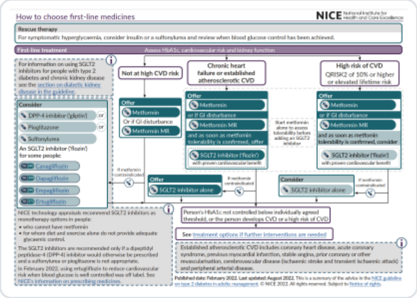

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment
Assess HbA1c, cardiovascular risk and kidney function
Not at high CVD risk
Chronic heart failure or established atherosclerotic CVD
High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
Or if GI disturbance
Metformin MR
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin')
with proven cardiovascular benefit
Start metformin alone to assess tolerability before adding an SGLT2 inhibitor
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin')
with proven cardiovascular benefit
If metformin contraindicated
Offer
SGLT2 inhibitor alone
If metformin contraindicated
Consider
SGLT2 inhibitor alone
If metformin contraindicated
Consider
DPP-4 inhibitor ('gliptin')
or
Pioglitazone
or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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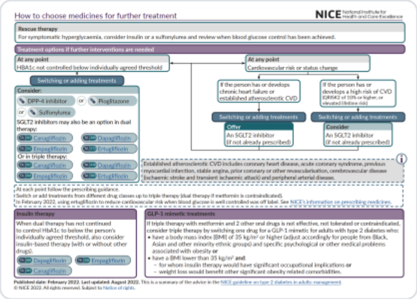

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed
At any point
HBA1c not controlled below individually agreed threshold
Switching or adding treatments
Consider:
DPP-4 inhibitor
or
Pioglitazone
or
Sulfonylurea
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
At any point
Cardiovascular risk or status change
If the person has or develops chronic heart failure or established atherosclerotic CVD
If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

SGLT2 inhibitors may also be an option in dual therapy:

Or in triple therapy:

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

Dapagliflozin Empagliflozin Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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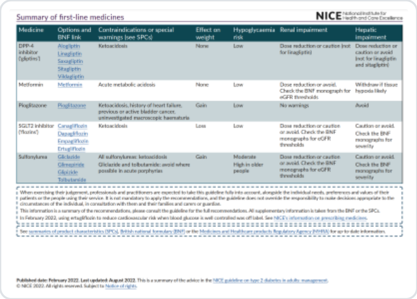

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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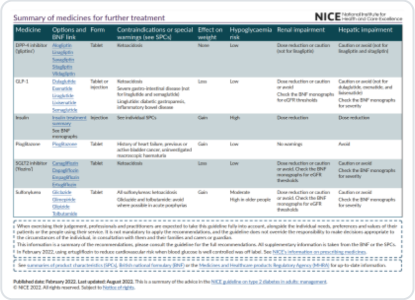

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

Published date: February 2022. Last updated: August 2022. This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

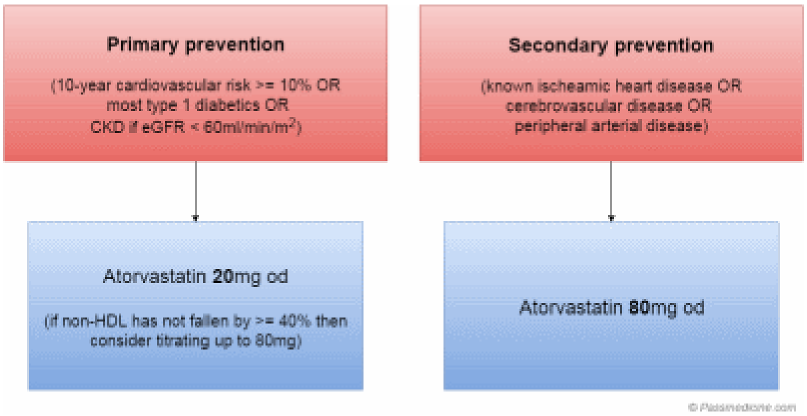
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

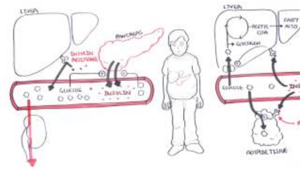
NICE

2022 Type 2 diabetes guidelines

👍 8 👎 5

Report broken link

Media

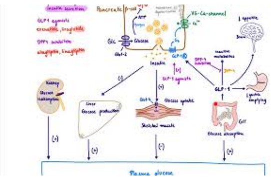


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

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Score: **23.7%**

1 ✓

2 ✓

3 ✓

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Question 288 of 414 ✗

A 53-year-old woman is reviewed in the endocrinology clinic. She complains of episodes of anxiety, palpitations, clamminess, hunger, and nausea. These episodes are not related to meals. She is asked to record her blood sugars during these episodes, and it is found to range between 2.8-3.3mmol/L. Outwith these episodes her blood sugar is between 3.5-5.5.

There is no past medical history and the patient takes no regular medications.

What investigation is most likely to be diagnostic?

	Oral glucose tolerance test	7%
	Serum C-peptide levels	33%
🟥	Short synacthen test	10%
🟩	Supervised fasting	48%
	Water deprivation test	1%

Insulinoma is diagnosed with supervised prolonged fasting

Important for me Less important

Supervised fasting is correct. This patient has symptoms suggestive of insulinoma. The fact these symptoms occur unrelated to meals is further suggestive. Diagnosis is by the supervised fasting test.

Oral glucose tolerance test is incorrect. This is a test for diabetes mellitus, used if fasting glucose results are inconclusive or if the patient is pregnant. The symptoms described in this case are of hypoglycaemia, of which insulinoma is a potential cause. The fact that the episodes occur at times unrelated to meals further suggests insulinoma. The diagnostic test for this is 48 or 72-hour supervised fasting.

Serum C-peptide levels is incorrect. The symptoms described in this case are of hypoglycaemia, of which insulinoma is a potential cause. High levels of C-peptide do not diagnose insulinoma, they simply indicate that high levels of endogenous insulin are being produced.

Short synacthen test is incorrect. This is a test for adrenal insufficiency. The symptoms described in this case coupled with the low blood sugar readings are not explained by adrenal insufficiency.

Water deprivation test is incorrect. The water deprivation test is used to diagnose diabetes insipidus. This would present with polyuria and polydipsia, but would not explain the episodes of hypoglycaemia described here.

👍 👎 Discuss (1) Improve

Next question

Insulinoma ★

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics
- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

Features
- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis
- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Management
- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

Next question

Textbooks

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Media

Pancreatic
Neuroendocrine
Neoplasms

Pancreatic neuroendocrine neoplasms

Osmosis - YouTube 👍 19 👎 0

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Score: **23.6%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓

PassMedicine

← Question 289 of 414 ✗ ⚐ →

Each one of the following is seen in Klinefelter's syndrome, except:

	Small, firm testes	6%
	Lack of secondary sexual characteristics	8%
🟥	Infertility	2%
	Increased incidence of breast cancer	27%
🟩	Reduced gonadotrophin levels	56%

Klinefelter's syndrome - elevated gonadotrophin levels

Important for me Less important

👍 👎 Discuss (2) Improve

Next question

Klinefelter's syndrome ★

Klinefelter's syndrome is associated with karyotype 47, XXY.

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels but low testosterone

Diagnosis is by karyotype (chromosomal analysis).

Next question

Textbooks

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Media

KLINEFELTER
SYNDROME

Klinefelter syndrome

Osmosis - YouTube 👍 13 👎 0

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Score: **23.5%**

1	✓
2	✓
3	✓
4	✗
5	✗

PassMedicine

Question 290 of 414 ✗

A 35-year-old woman attends the rheumatology clinic. She has Raynaud's syndrome and is under investigation for potential secondary causes. Her only other significant past medical history is previous renal stones.

She has some blood tests taken as part of this investigative workup:

Na^+	137 mmol/L	(135 - 145)
K^+	3.1 mmol/L	(3.5 - 5.0)
Bicarbonate	14 mmol/L	(22 - 29)
Cl^-	119 mmol/L	(98-107)
Urea	5.4 mmol/L	(2.0 - 7.0)
Creatinine	66 µmol/L	(55 - 120)

Urine biochemistry is also performed:

pH	5.8 µmol/L	(<5.5)

What is the most likely explanation for these biochemistry results?

Distal renal tubular acidosis	67%
Hypoaldosteronism/aldosterone insensitivity renal tubular acidosis	6%
Membranous renal tubular acidosis	2%
Mixed renal tubular acidosis	4%
Proximal renal tubular acidosis	20%

Distal renal tubular acidosis can cause calcium phosphate renal stones and is linked to Sjogrens syndrome

Important for me Less important

Distal renal tubular acidosis is correct. Distal renal tubular acidosis is due to a failure of H^+ secretion in the distal convoluted tubule. This results in blood acidosis and a resultant hypokalaemia. Renal stone formation is then the result of alkalinisation of the urine, which favours calcium phosphate stone formation. Urinary pH is usually above 5.5.

Hypoaldosteronism/aldosterone insensitivity renal tubular acidosis is incorrect. This is due to a deficiency or resistance to aldosterone. This results in mild blood acidosis and *hyper*kalaemia. The potassium in this case is low, so this option is incorrect.

Membranous renal tubular acidosis is incorrect. There is no such thing as membranous renal tubular acidosis; 'membranous' is a type of glomerulonephritis.

Mixed renal tubular acidosis is incorrect. Mixed renal tubular acidosis is not seen anymore. It was observed in the 1960s and 1970s in children and presented as a combination of distal and proximal renal tubular acidosis.

Proximal renal tubular acidosis is incorrect. Proximal renal tubular acidosis is due to a failure of bicarbonate reabsorption in the proximal tubule. This results in blood acidosis and a resultant hypokalaemia, as well as the presence of bicarbonate ions in the urine. The urinary pH in proximal renal tubular acidosis is usually below 5.5, hence why this answer is incorrect. This is because in proximal renal tubular acidosis, the intercalated cells of the distal convoluted tubule are still functional, and can still secrete H^+ to acidify the urine beyond a pH of 5.5. Proximal renal tubular acidosis is also less likely to result in calcium phosphate renal stone formation than distal renal tubular acidosis.

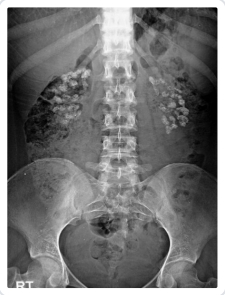
👍 👎 Discuss Improve

Next question

Renal tubular acidosis ★

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)
- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule
- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

Textbooks

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Question 291 of 414 ×

A 58-year-old woman presents with a high fever, severe agitation, confusion, profuse sweating, and palpitations. Observations show a temperature of 40°C, heart rate 160 bpm, blood pressure 190/100 mmHg and respiratory rate 24 breaths/min. Bloods are performed:

Hb	120 g/L	Male: (135-180) Female: (115 - 160)
Platelets	362 * 10^9/L	(150 - 400)
WBC	14.8 * 10^9/L	(4.0 - 11.0)
Calcium	2.7 mmol/L	(2.1-2.6)
Phosphate	1.2 mmol/L	(0.8-1.4)
Thyroid-stimulating hormone (TSH)	< 0.01 mU/L	(0.5-5.5)
Free thyroxine (T4)	48 pmol/L	(9.0 - 18)

She is started on propranolol, intravenous fluids, and propylthiouracil.

What other treatment is indicated?

🟥	Carbimazole	10%
🟩	Hydrocortisone	70%
	Levothyroxine	2%
	Prednisolone	14%
	Thyroidectomy	4%

Thyrotoxic storm is treated with beta blockers, propylthiouracil and hydrocortisone

Important for me Less important

Based on the clinical presentation, and thyroid function tests, the patient most likely has a thyroid storm. This is a medical emergency with an untreated mortality of 20-30%. As such, the patient requires urgent treatment and consideration for level 2 care. **Hydrocortisone** is correct - intravenous hydrocortisone therapy should be initiated to reduce peripheral conversion of T4 to the more active T3 hormone.

Carbimazole is incorrect. This is an anti-thyroid medication. Since the patient has been started on propylthiouracil, carbimazole should not be used.

Levothyroxine is incorrect. The patient has hyperthyroidism, so levothyroxine is not indicated.

Prednisolone is incorrect. Hydrocortisone is preferred since it has both glucocorticoid and mineralocorticoid effects, providing a broader anti-inflammatory and supportive hormonal coverage compared to prednisone.

Thyroidectomy is incorrect. A thyroidectomy is not indicated in the acute management of a thyroid storm.

👍 👎 Discuss (1) Improve

Next question

Thyroid storm

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating events:

- thyroid or non-thyroidal surgery
- trauma
- infection
- acute iodine load e.g. CT contrast media

Clinical features include:

- fever > 38.5ºC
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test - jaundice may be seen clinically

Management:

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- beta-blockers: typically IV propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

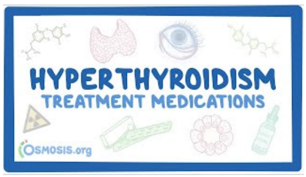
Next question

Textbooks

High-yield textbook

Extended textbook

Media


HYPERTHYROIDISM
TREATMENT MEDICATIONS
Osmosis.org

Hyperthyroidism treatment medications

Osmosis - YouTube 👍 5 👎 0

THYROID
STORM

Thyroid storm

Osmosis - YouTube 👍 3 👎 2

PassMedicine

Question 292 of 414 ✗

A 39-year-old woman is reviewed in the clinical pharmacology clinic following referral by her GP for management of her hypertension. She has a blood pressure of 159/90 mmHg despite 3 oral anti-hypertensive medications including full dose ramipril. Examination in the clinic confirms the elevated blood pressure. Her pulse is 72 and regular. Her chest is clear and her abdomen is soft and non-tender with no palpable masses. Her body mass index is 28 kg/m².

Hb	130 g/l
Platelets	221 * 10^9/l
WBC	6.0 * 10^9/l

Na^+	141 mmol/l
K^+	3.1 mmol/l
Bicarbonate	31 mmol/l
Urea	4.1 mmol/l
Creatinine	102 µmol/l
Calcium	2.45 mmol/l

CT abdomen: Right adrenal adenoma, thick walled gallbladder with a solitary stone

Which of the following is the most likely diagnosis?

🟩	Conn's syndrome	71%
	Cushing's syndrome	11%
🟥	Essential hypertension	1%
	Phaeochromocytoma	13%
	Renal artery stenosis	4%

Primary hyperaldosteronism can present with hypertension, hypernatraemia, and hypokalemia

Important for me Less important

The relatively normal weight, coupled with hypertension and hypokalaemic metabolic alkalosis fits well with a diagnosis of Conn's syndrome, (primary hyperaldosteronism). The right adrenal adenoma is the likely source of excess aldosterone production. In the presence of an ACE inhibitor prescribed for hypertension, significant hypokalaemia is very likely to be related to Conn's.

Cushing's syndrome is unlikely given that the body mass index is only slightly elevated, and the presence of an adrenal adenoma and biochemical abnormalities effectively rules out essential hypertension. Phaeochromocytoma may be associated with hypokalaemia, but is more likely to be associated with episodic hypertension associated with bursts of catecholamine release. In renal artery stenosis, a significant rise in creatinine would be expected in association with the introduction of the ramipril.

👍 | 👎 | Discuss (10) | Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes

- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

Features

- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness

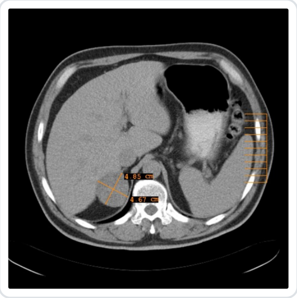
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
  - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



Next question

Textbooks

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Extended textbook

Links

The Endocrine Society 👍 5 👎 3

2016: The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment

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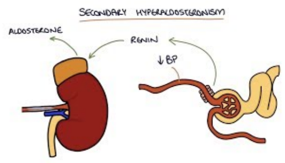
Media


SECONDARY HYPERALDOSTERONISM
ALDOSTERONE
RENIN
↓BP

Hyperaldosteronism and Conn's Syndrome

Zero To Finals - YouTube 👍 47 👎 5

HYPERALDOSTERONISM

Hyperaldosteronism - causes, symptoms, diagnosis, treatment, pathology

Osmosis - YouTube 👍 43 👎 6

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Score: **23.3%**

1 ✓
2 ✓
3 ✓
4 ✗

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← Question 293 of 414 ✗ ⚐ →

A 45-year-old woman with Graves' disease comes for review. She has recently been diagnosed with thyroid eye disease and is being considered for radiotherapy. Over the past three days her right eye has become red and painful. On examination there is proptosis and erythema of the right eye. Visual acuity is 6/9 in both eyes. What complication is she most likely to have developed?

🟩	Exposure keratopathy	70%
	Optic neuropathy	17%
	Carbimazole-related neutropaenia	4%
	Central retinal vein occlusion	6%
🟥	Sjogren's Syndrome	3%

Exposure keratopathy is the most common complication of thyroid eye disease

Important for me Less important

The most likely complication of thyroid eye disease is exposure keratopathy. This complication arises primarily due to the proptosis of the eyeballs and eyelid retraction associated with the condition, which can lead to difficulty in completely closing the eyes. As a result, the corneas are more exposed to the environment and can become dry and irritated.

The following factors contribute to the development of exposure keratopathy:

- Eyelid retraction: One of the hallmark features of thyroid eye disease is retraction of the upper and/or lower eyelids. This retraction can lead to increased exposure of the cornea, the clear front surface of the eye.
- Proptosis: thyroid eye disease can cause the eye muscles and fat to swell, pushing the eyeball forward. This protrusion can prevent the eyelids from closing properly, further exposing the cornea.
- Reduced tear film: The inability to close the eyelids fully, combined with potential inflammation in the tear glands, can reduce the protective tear film that coats the cornea, leading to dryness and irritation.
- Corneal damage: Continuous exposure and dryness can lead to damage of the corneal surface, resulting in exposure keratopathy. Symptoms might include pain, redness, tearing,

sensitivity to light, and in severe cases, vision impairment.
- Risk of ulceration and infection: If exposure keratopathy is not managed effectively, the cornea can develop ulcers and become more prone to infections, which could lead to more serious complications, including vision loss.

👍 | 👎 | 💬 Discuss (3) | Improve

Next question

Thyroid eye disease ★

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

Pathophysiology
- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

Prevention
- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

Features
- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eyelids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

Management
- smoking cessation
- topical lubricants may be needed to help prevent corneal inflammation caused by exposure

- steroids
- radiotherapy
- surgery

Complications

Exposure keratopathy
- this is the most common complication of thyroid eye disease
- due to eyelid retraction and proptosis (exophthalmos) → cornea becomes excessively exposed, disrupting the normal tear film → dryness, irritation, and corneal ulceration
- symptoms include foreign body sensation, pain, and photophobia
- in severe cases, it can lead to corneal scarring and vision impairment.

Optic neuropathy
- one of the most serious complications of thyroid eye disease
- occurs when enlarged extraocular muscles compress the optic nerve at the apex of the orbit → a reduction in visual acuity, colour vision deficits, and visual field defect
- it requires urgent medical intervention to prevent permanent vision loss.

Strabismus and diplopia
- fibrosis and enlargement of the extraocular muscles can result in restrictive strabismus → misalignment of the eyes → double vision (diplopia)
- this not only affects visual function but can also significantly impair the quality of life.

Monitoring patients with established thyroid eye disease

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):
- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

Next question

PassMedicine

Question 294 of 414 ✓

A 34-year-old female with a history of Addison's disease presents for review in endocrinology clinic. She is generally well but complains of a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause?

Adverse effect of hydrocortisone therapy	18%
11-hydroxylase deficiency	23%
Diethylstilbestrol deficiency	2%
Oestrogen deficiency	10%
Dehydroepiandrosterone (DHEA) deficiency	48%

Dehydroepiandrosterone is the most abundant circulating adrenal steroid. Adrenal glands are the main source of dehydroepiandrosterone in females - loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido. Research is ongoing as to whether routine replacement of DHEA is beneficial

Discuss (2) Improve

Next question

Addison's disease

Autoimmune destruction of the adrenal glands is the most common cause of primary hypoadrenalism in the UK, accounting for 80% of cases. This is termed Addison's disease and results in reduced cortisol and aldosterone being produced.

Features
- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases)
    - ACTH is derived from a larger precursor molecule called proopiomelanocortin (POMC). When POMC is cleaved to produce ACTH, other melanocyte-stimulating hormones

  (MSH) are also produced. These MSHs have the effect of stimulating melanocytes in the skin to produce more melanin, the pigment responsible for skin colour
  - primary Addison's is associated with hyperpigmentation whereas secondary adrenal insufficiency is not
- vitiligo
- loss of pubic hair in women
- hypotension
- hypoglycaemia
- hyponatraemia and hyperkalaemia may be seen
- crisis: collapse, shock, pyrexia

Other causes of hypoadrenalism

Primary causes
- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

Secondary causes
- pituitary disorders (e.g. tumours, irradiation, infiltration)

Exogenous glucocorticoid therapy

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 2 👎 0

Addison's disease

Royal College of Physicians 👍 4 👎 2

2017 Adrenal insufficiency â€” recognition and management

Report broken link

Media

ADDISON'S DISEASE

Addison's disease

Armando Hasudungan - YouTube 👍 30 👎 2

Primary adrenal insufficiency (Addison's disease)

Osmosis - YouTube 👍 13 👎 5

Report broken media

Score: **23.5%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗

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Question 295 of 414 ✗

A 72-year-old man is reviewed in the diabetes clinic. He has a history of heart failure and type 2 diabetes mellitus. His current medications include furosemide 40mg od, ramipril 10mg od and bisoprolol 5mg od. Clinical examination is unremarkable with no evidence of peripheral oedema, a clear chest and blood pressure of 130/76 mmHg. Recent renal and liver function tests are normal. Which one of the following medications is contraindicated?

Sitagliptin	5%
Pioglitazone	77%
Gliclazide	8%
Exenatide	7%
Metformin	4%

Pioglitazone - contraindicated by: heart failure

Important for me Less important

The correct answer is **Pioglitazone**. Pioglitazone is a thiazolidinedione that acts as an insulin sensitiser by activating peroxisome proliferator-activated receptor gamma (PPARÎ³). However, it has been found to cause fluid retention and exacerbate heart failure, hence it is contraindicated in patients with heart failure. This patient's history of heart failure makes pioglitazone unsuitable.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that works by increasing levels of incretin hormones, enhancing the secretion of insulin, and reducing glucagon release. It does not cause fluid retention or worsen heart failure.

Gliclazide is a second-generation sulfonylurea used for the treatment of type 2 diabetes. It stimulates the pancreas to secrete more insulin but does not have any significant cardiac side effects or contraindications in heart failure.

Exenatide is a glucagon-like peptide-1 (GLP-1) agonist. It enhances glucose-dependent insulin secretion and suppresses inappropriate glucagon secretion, slowing gastric emptying and promoting satiety. There are no specific contraindications related to heart failure.

Finally, **Metformin**, a biguanide anti-diabetic medication, works by decreasing hepatic glucose production and increasing insulin sensitivity in peripheral tissues. Contraindications include renal impairment due to the risk of lactic acidosis but it's not specifically contraindicated in heart failure; indeed, recent guidelines suggest its use may be beneficial unless associated with hypoperfusion or hypoxaemia.

Discuss (3) Improve

Next question

Thiazolidinediones

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. It's natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

Next question

Textbooks

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Question 296 of 414 ✗

A 67-year-old man is discharged after having a percutaneous coronary intervention following an acute coronary syndrome (ACS). He had no past medical of note prior to the ACS. Which type of lipid modification therapy should he have been started on during the admission?

	Simvastatin 40mg on	2%
	Atorvastatin 10mg on	1%
	Atorvastatin 20mg on	8%
🟥	Atorvastatin 40mg on	14%
🟩	Atorvastatin 80mg on	75%

Patients with established cardiovascular disease (e.g. IHD, stroke, PVD) should take high-intensity statin therapy (e.g. atorvastatin 80mg) regardless of baseline lipid profile

Important for me Less important

The correct answer is **Atorvastatin 80mg**. According to the UK guidelines, a high-intensity statin such as Atorvastatin 80mg should be initiated in patients who have had an acute coronary syndrome (ACS) regardless of their baseline cholesterol levels. This is because high-intensity statins have been shown to provide a greater reduction in low-density lipoprotein cholesterol (LDL-C) levels and subsequently reduce the risk of further cardiovascular events.

The other options are not appropriate for this patient:

Simvastatin 40mg is a moderate-intensity statin and would not provide the same level of LDL-C reduction as a high-intensity statin like Atorvastatin 80mg. Therefore, it is not the optimal choice for lipid modification therapy following an ACS.

Atorvastatin 10mg and **Atorvastatin 20mg** are lower doses of Atorvastatin and would also be considered moderate-intensity statins. These doses would not provide the same level of LDL-C reduction as Atorvastatin 80mg, so they are not recommended for this patient either.

Atorvastatin 40mg, although being a higher dose than the previously mentioned options, still does not offer the same level of LDL-C reduction as Atorvastatin 80mg. It may be used in some circumstances where there are contraindications or intolerance to higher doses; however, it is not the first-line choice for this patient after an ACS.

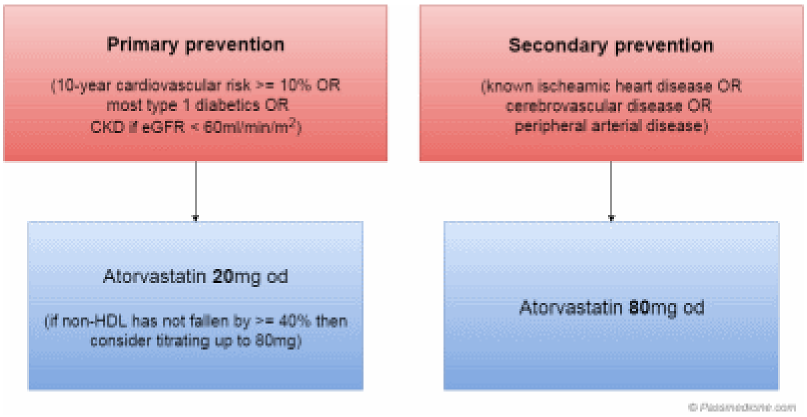
In summary, the best lipid modification therapy for this patient after an acute coronary syndrome would be **Atorvastatin 80mg**, as it provides optimal LDL-C reduction to reduce the risk of further cardiovascular events according to UK guidelines.

👍 👎 Discuss (2) Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m^2)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria

- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake

- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation

- smokers should be encouraged to quit

Next question

Textbooks

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Question 297 of 414 ✓

A 49-year-old woman with type 2 diabetes mellitus is being considered for exenatide therapy. Which one of the following is not part of the NICE criteria for starting or continuing this drug?

BMI > 35 kg/m^2	10%
Greater than 1.0 percentage point HbA1c reduction after 6 months	15%
Has failed with insulin therapy	51%
Has type 2 diabetes mellitus	7%
Weight loss > 3% at 6 months	17%

Patients do not need to have been on insulin prior to using exenatide

Discuss (2) Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

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Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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Media

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Question 298 of 414 ✗

A 40-year-old woman is seen in the endocrinology clinic with a 4-week history of milky nipple discharge. There is no history of breast pain or fever. She also complains of intermittent abdominal pain and constipation despite drinking plenty of water and eating a high fibre diet. Her past medical history includes gastric reflux for which she takes lansoprazole daily. She takes no other medications and has no allergies.

Investigations:

Hb	122 g/L	(115 - 160)
Platelets	223 * 10^9/L	(150 - 400)
WBC	6.3 * 10^9/L	(4.0 - 11.0)
Na^+	136 mmol/L	(135 - 145)
K^+	4.1 mmol/L	(3.5 - 5.0)
Urea	6.1 mmol/L	(2.0 - 7.0)
Creatinine	110 µmol/L	(55 - 120)
Calcium	2.8 mmol/L	(2.1-2.6)
Phosphate	1.2 mmol/L	(0.8-1.4)
Magnesium	0.9 mmol/L	(0.7-1.0)
B-HCG	< 1 mIU/mL	(< 1 mIU/mL)

What is the most likely diagnosis?

Pituitary adenoma	20%
🟥 Von-Hippel-Lindau syndrome	4%
🟩 Multiple endocrine neoplasia type 1	67%
Multiple endocrine neoplasia type 2a	7%
Multiple endocrine neoplasia type 2b	3%

Peptic ulceration, galactorrhoea, hypercalcaemia - multiple endocrine neoplasia type I

Important for me Less important

This patient has multiple endocrine neoplasia (MEN) type 1. MEN type 1 is associated with hyper**p**arathyroidism, **p**ituitary disease and **p**ancreatic disease such as insulinomas or gastrinomas. This patient has evidence of hypercalcaemia from her laboratory tests and symptoms of constipation and abdominal pain. Her abdominal pain may also be exacerbated by likely underlying peptic ulcer disease for which she is taking lansoprazole. Galactorrhoea is the term given to a milky nipple discharge that arises secondary to excess prolactin.

A pituitary adenoma would explain this patient's galactorrhoea as commonly pituitary disease is secondary to prolactinomas. A raised prolactin level stimulates milk production in the breast tissue. However, a pituitary adenoma alone would not explain her hypercalcaemia and gastric disease.

Von-Hippel-Lindau syndrome is an autosomal dominant disorder characterised by multiple visceral cysts affecting the central nervous system, kidneys, pancreas, adrenal glands, liver and lung. The most common presenting features are haemangioblastomas are seen in the brain, spinal cord and retina causing headaches, neurological disturbance and visual changes. These symptoms do not reflect what are seen in the question stem and suggest an alternative diagnosis.

MEN type 2a is characterised by **p**haeochromocytoma and hyper**p**arathyroidism. Typically, such patients may be hypertensive and have symptoms of excess sympathetic drive such as tachycardia, sweating and flushes. It does not explain her galactorrhoea or symptoms of peptic ulcer disease.

MEN type 2b is associated with **p**haeochromocytoma along with a marfanoid body habitus and neuromas. Medullary thyroid carcinoma is also associated with MEN type 2a and 2b.

👍 👎 Discuss (4) Improve

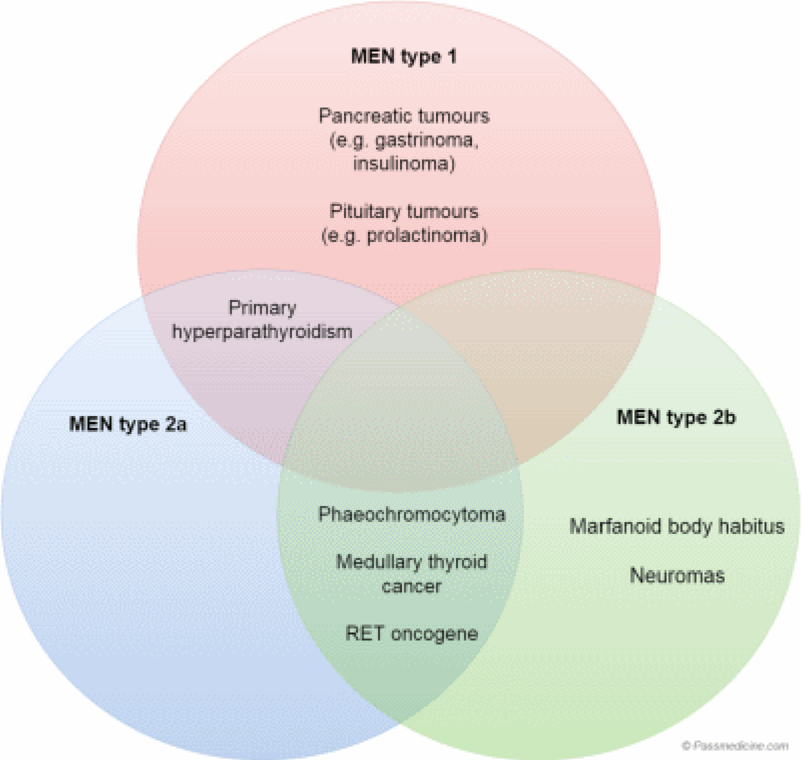
Next question

Multiple endocrine neoplasia ★

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s	Medullary thyroid cancer (70%)	Medullary thyroid cancer

MEN type I	**MEN type IIa**	**MEN type IIb**
Parathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
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Venn diagram showing the different types of MEN and their associated features

Next question

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Question 299 of 414 ✓

A 40-year-old male known diabetic presents with increasing headaches and visual issues.

On examination, he has enlargement of the hands and feet, coarse facial features and splaying of the teeth.

What is the most appropriate first-line investigation?

Oral glucose tolerance test (OGTT) with serial GH measurements	21%
Pituitary MRI	8%
Random serum growth hormone (GH) level	4%
Serum growth hormone-releasing hormone (GHRH) level	4%
Serum insulin-like growth factor 1 (IGF-1)	62%

Serum IGF-1 levels are now the first-line test for acromegaly

Important for me Less important

Serum IGF-1 is the correct answer as The Endocrine Society guidelines now suggested IGF-1 measurement as the first-line test in patients presenting with typical clinical manifestations of acromegaly.

OGTT with serial GH measurements is incorrect as this is no longer the suggested first-line test for acromegaly. The Endocrine Society recommends in patients with clinically suspected acromegaly, and an elevated or equivocal serum IGF-1 level, the diagnosis should then be confirmed by finding a lack of GH suppression with an OGTT.

Pituitary MRI is incorrect as although this may demonstrate a pituitary tumour this is not the recommended first-line investigation to diagnose acromegaly.

A random serum GH level is incorrect as GH levels vary throughout the day and therefore cannot be used to confirm acromegaly.

Serum GHRH level is not the first-line test as the vast majority of acromegaly cases are due to pituitary adenomas. Acromegaly secondary to GHRH secreting tumours are rare and should only be investigated for cases where a pituitary defect cannot be confirmed.

👍 👎 Discuss (3) Improve

Next question

Acromegaly: investigations ★

Growth hormone (GH) levels vary during the day and are therefore not diagnostic.

Serum IGF-1 levels have now overtaken the oral glucose tolerance test (OGTT) with serial GH measurements as the first-line test. The OGTT test is recommended to confirm the diagnosis if IGF-1 levels are raised.

The Endocrine Society guidelines suggest the following:

> *1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features.*
> ...
> *1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 µg/L following documented hyperglycemia during an oral glucose load.*

Serum IGF-1 may also be used to monitor disease

Oral glucose tolerance test
- in normal patients GH is suppressed to < 2 mu/L with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour.

Next question

Textbooks

High-yield textbook

Extended textbook

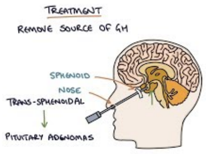
Links

The Endocrine Society 👍 8 👎 0

2014 Acromegaly guidelines

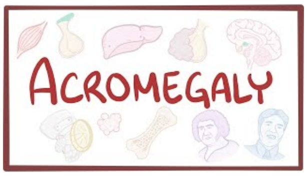
Report broken link

Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 12 👎 1


ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 6 👎 1

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Question 300 of 414 ✗

A 32-year-old man with familial hypercholesterolaemia comes to the lipid clinic for review. Despite 80mg of atorvastatin, his LDL cholesterol is still 3.8 and he suffered an inferior myocardial infarction some 3 months earlier. You elect to commence evolocumab.

Which of the following reflects the mode of action of evolocumab?

	Activates lipoprotein lipase	12%
	Blocks absorption of cholesterol in the GI tract	10%
	Inhibits PPAR-alpha	9%
🟥	Inhibits SGLT-1	2%
🟩	Prevents PCSK9-mediated LDL receptor degradation	67%

Evolocumab prevents PCSK9-mediated LDL receptor degradation. Evolocumab binds selectively to PCSK9 and prevents circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-cholesterol. Use of evolocumab is associated with a reduction in levels of free PCSK9 and this is taken as a measure of target engagement. it lowers LDL cholesterol by more than 50% in 85% of patients who are treated.

Fibrates increase lipoprotein lipase activity via PPAR-alpha agonism, and ezetimibe reduces intestinal absorption of cholesterol. SGLT-1 inhibitors reduce intestinal absorption of glucose.

Use of evolocumab is endorsed by NICE under certain conditions only, namely that the dosage is 140mg every 2 weeks and LDL cholesterol is persistently above 3.5 mmol/l.

https://www.nice.org.uk/guidance/ta394/chapter/1-recommendations

Discuss (5) Improve

Next question

Familial hypercholesterolaemia ★

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Case finding:

- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
    - a total cholesterol level greater than 7.5 mmol/l and/or
    - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:
    - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
    - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Next question

Textbooks

High-yield textbook

Extended textbook

Links

The FH Foundation 👍 3 👎 1

Simon Broom Criteria

The FH Foundation 👍 3 👎 1

High cholesterol during preganancy

NICE 👍 3 👎 1

2008 Familial hypercholesterolaemia guidelines

Public Library of Science (PLoS) 👍 2 👎 1

Cascade Screening for Familial Hypercholesterolemia (FH)

Report broken link

Media

FAMILIAL
HYPERCHOLESTEROLEMIA
Osmosis.org

Familial hypercholesterolaemia

Osmosis - YouTube

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Question 301 of 414 ✗

A 32-year-old woman presents to her GP surgery as she has missed her last period. A pregnancy test confirms that she is pregnant, and it is estimated that she is 6 weeks pregnant. She is well, but has hypothyroidism and takes 150 mcg levothyroxine.

What is the single best advice regarding her medication?

	Keep the same dose of levothyroxine	13%
	Decrease levothyroxine by 50 mcg	4%
🟩	Increase levothyroxine by 50 mcg	71%
🟥	Decrease levothyroxine by 100 mcg	1%
	Increase levothyroxine by 100 mcg	12%

Women with hypothyroidism may need to increase their thyroid hormone replacement dose by up to 50% as early as 4-6 weeks of pregnancy

Important for me Less important

In pregnancy, anyone already on levothyroxine treatment should increase their dose. Thyroid doses should be adjusted in steps of 25-50mcg. In pregnancy, the increase in thyroid replacement is typically 20-50%, which normally equates to 25mcg-50mcg increase.

Thyroid-stimulating hormone levels (TSH) should be measured during each trimester and doses adjusted accordingly, bearing in mind the trimester-specific ranges for TSH. Following delivery, levothyroxine should be reduced to the patient's preconception dose with repeat TFTs at 6 weeks post-partum.

As this woman is already on levothyroxine it would be appropriate to increase the dose and arrange thyroid-stimulating hormone (TSH) blood tests. There is an increased risk of fatal complications if the dose is kept the same.

It would not be appropriate to decrease the levothyroxine dose, as inadequate thyroid replacement is associated with increased complications in pregnancy.

Increasing levothyroxine by 100mcg initially would be too much, as excessive replacement can be detrimental to the fetus. It is most appropriate to start with small increments of 25-50mcg and then adjust the dose further based on the TSH results.

👍 👎 Discuss (2) Improve

Next question

Pregnancy: thyroid problems

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management

- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
  - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

Score: **23.6%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗

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Question 302 of 414 ✓

At which point in the menstrual cycle do progesterone levels peak?

Luteal phase ✓	65%
Ovulation	14%
Follicular phase	15%
Levels remain constant throughout cycle	1%
Menstruation	5%

Progesterone is secreted by the corpus luteum following ovulation.

Discuss (2) Improve

Next question

Menstrual cycle

The menstrual cycle may be divided into the following phases:

	Days
Menstruation	1-4
Follicular phase (proliferative phase)	5-13
Ovulation	14
Luteal phase (secretory phase)	15-28

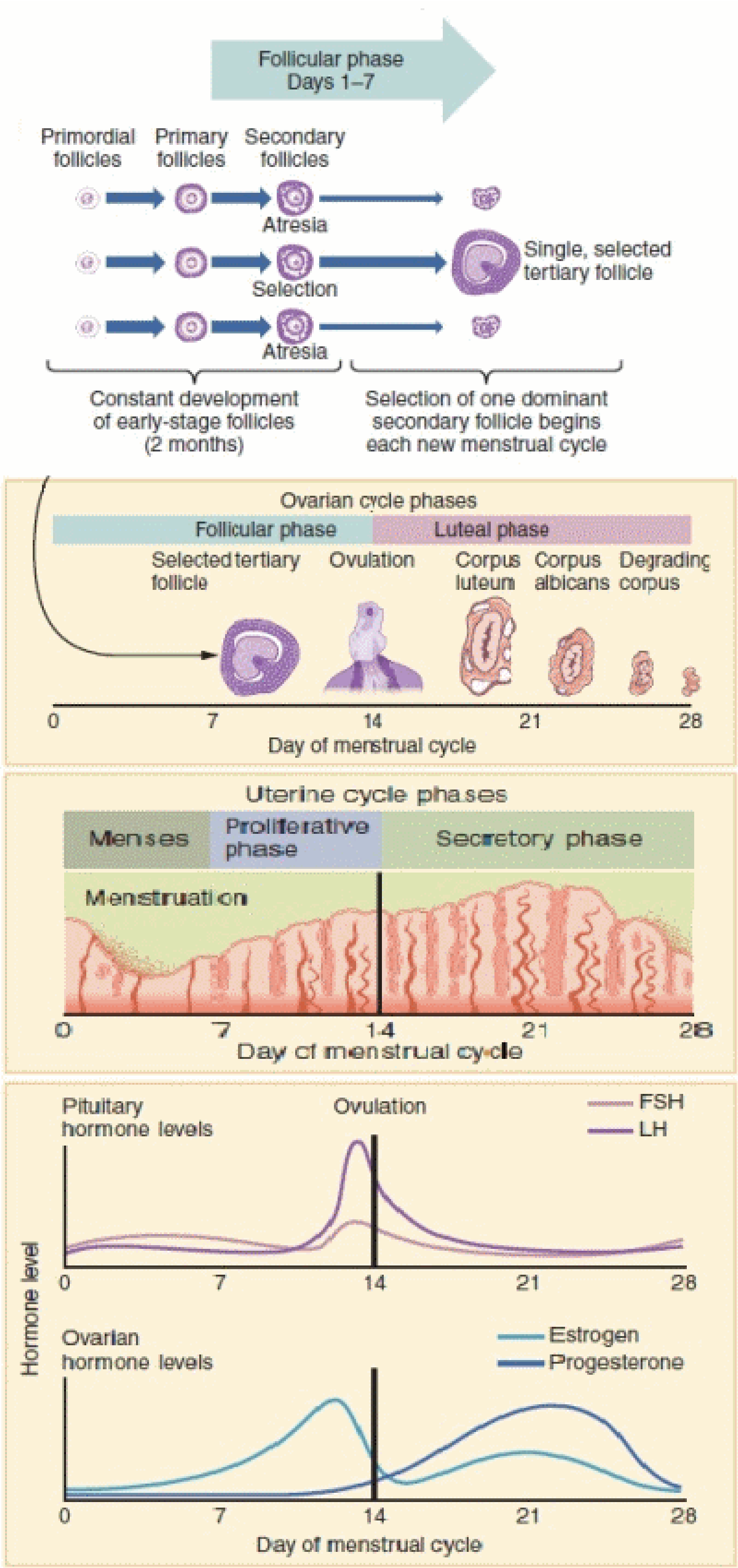
Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Selection
Atresia
Single, selected tertiary follicle
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle
Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle
Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle
Pituitary hormone levels
Ovulation
FSH
LH
0
7
14
21
28
Hormone level
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

Image sourced from Wikipedia

Further details are given in the table below

	Follicular phase (proliferative phase)	Luteal phase (secretory phase)
Ovarian histology	A number of follicles develop. One follicle will become dominant around the mid-follicular phase	Corpus luteum
Endometrial histology	Proliferation of endometrium	Endometrium changes to secretory lining under influence of progesterone
Hormones	A rise in FSH results in the development of follicles which in turn secrete oestradiol When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation	Progesterone secreted by corpus luteum rises through the luteal phase. If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall Oestradiol levels also rise again during the luteal phase
Cervical mucus	Following menstruation the mucus is thick and forms a plug across the external os Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit	Under the influence of progesterone it becomes thick, scant, and tacky
Basal body temperature	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels

Next question

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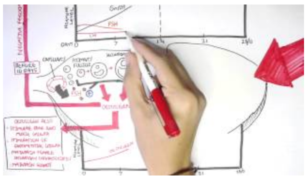
Links

Wikipedia 👍 2 👎 1

Menstrual cycle (including diagram)

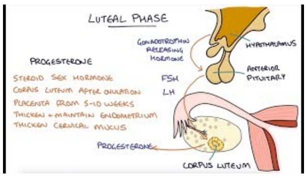
Report broken link

Media



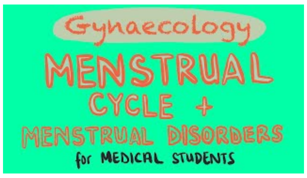
Female Reproductive System - Menstrual Cycle, Hormones and Regulation

Armando Hasudungan - YouTube 👍 21 👎 1


LUTEAL PHASE
PROGESTERONE
STEROID SEX HORMONE
CORPUS LUTEUM AFTER OVULATION
PLACENTA FROM 5-10 WEEKS
THICKEN + MAINTAIN ENDOMETRIUM
THICKEN CERVICAL MUCUS
GONADOTROPHIN RELEASING HORMONE
HYPOTHALAMUS
ANTERIOR PITUITARY
FSH
LH
PROGESTERONE
CORPUS LUTEUM

Understanding the Menstrual Cycle

Zero to Finals - YouTube 👍 8 👎 1


Gynaecology
MENSTRUAL CYCLE +
MENSTRUAL DISORDERS
for MEDICAL STUDENTS

Menstrual Cycle + Menstrual Disorders For Medical Students

MedFlix - YouTube 👍 4 👎 1

PassMedicine

Question 303 of 414 ✗

A 40-year-old Afro-Caribbean woman presents with menorrhagia, she states she passes large clots for 7 days every month and feels general fatigue. More recently she has felt an intermittent headache, myalgia but denies any night sweats. She is currently two weeks since her last menstrual period. Her observations revealed a blood pressure of 135/82 mmHg heart rate 75/min, oxygen saturations 95% and temperature 36.5 °C.

On examination, there was a hard non-tender fixed mass in the supra-pubic region. She has no significant past medical conditions.

Blood results reveal:

Hb	190 g/L	Male: (135-180) Female: (115 - 160)
Hct	0.66 L/L	(0.4-0.52)
WCC	9.5×10^9	(4.0 - 11.0)
Platelets	500×10^9	(150 - 400)

JAK2 V617F mutation	-ve

Given this patient's presentation, what is the most likely cause of her blood results?

	Apparent polycythaemia	6%
	Chronic myeloid leukaemia	1%
🟥	Essential thrombocythaemia	5%
	Polycythaemia rubra vera	12%
🟩	Uterine fibroids	76%

Uterine fibroids may rarely be associated with secondary polycythaemia due to autonomous production of erythropoietin

Important for me Less important

Raised haemoglobin and haematocrit raises the suspicion of underlying polycythaemia as the cause for the raised haemoglobin. The onset of menorrhagia and suprapubic mass raises the suspicion that uterine fibroids may be cause for the polycythaemia.

Given that this patent has had her last period two weeks ago and her observations are within the normal range, she is unlikely to have apparent polycythaemia.

Her normal white cell count and lack of night sweats make chronic myeloid leukaemia less likely.

Her mildly raised platelet count is a product of her secondary polycythaemia and given her raised haemoglobin essential thrombocythaemia is unlikely.

The negative JAK2 V617F makes polycythaemia rubra vera less likely as 95% of patients with this condition will be positive for this mutation.

Discuss (3) Improve

Next question

Uterine fibroids ★

Fibroids are benign smooth muscle tumours of the uterus. They are thought to occur in around 20% of white and around 50% of black women in the later reproductive years.

Associations
- more common in Afro-Caribbean women
- rare before puberty, develop in response to oestrogen

Features
- may be asymptomatic
- menorrhagia
    - may result in iron-deficiency anaemia
- bulk-related symptoms
    - lower abdominal pain: cramping pains, often during menstruation
    - bloating
    - urinary symptoms, e.g. frequency, may occur with larger fibroids
- subfertility
- rare features:

    - polycythaemia secondary to autonomous production of erythropoietin

Diagnosis

- transvaginal ultrasound

Management

Asymptomatic fibroids

- no treatment is needed other than periodic review to monitor size and growth

Management of menorrhagia secondary to fibroids

- levonorgestrel intrauterine system (LNG-IUS)
    - useful if the woman also requires contraception
    - cannot be used if there is distortion of the uterine cavity
- NSAIDs e.g. mefenamic acid
- tranexamic acid
- combined oral contraceptive pill
- oral progestogen
- injectable progestogen

Treatment to shrink/remove fibroids

- medical
    - GnRH agonists may reduce the size of the fibroid but are typically used more for short-term treatment due to side-effects such as menopausal symptoms (hot flushes, vaginal dryness) and loss of bone mineral density
    - ulipristal acetate has been in the past but not currently due to concerns about rare but serious liver toxicity
- surgical
    - myomectomy: this may be performed abdominally, laparoscopically or hysteroscopically
    - hysteroscopic endometrial ablation
    - hysterectomy
- uterine artery embolization

Prognosis and complications

Fibroids generally regress after the menopause.

Some of the complications such as subfertility and iron-deficiency anaemia have been mentioned previously.

Other complications

- red degeneration - haemorrhage into tumour - commonly occurs during pregnancy

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 0 👎 0

Fibroids guidelines

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Media

UTERINE FIBROID
OSMOSIS.org

Uterine fibroids

Osmosis - YouTube 👍 6 👎 1

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PassMedicine

Question 304 of 414 ✗

An 81-year old female is admitted with a 6-week history dysphagia to both solids and liquids. She describes odynophagia, weight loss and night sweats.

On examination there was firm irregular mass in the right side of the anterior triangle of the neck. It was fixed, cold and painless. The mass moved with swallowing and you note a faint stridor like sound on inspiration. There was a further 3 irregular lymph nodes of note on palpation.

Bloods:

Thyroid stimulating hormone	4.5 mu/l
Free T4	12 pmol/l
Total T4	99 nmol/l

An ultrasound-guided biopsy is likely to reveal which histological tumour?

	Papillary	19%
	Follicular	10%
🟥	Medullary	9%
🟩	Anaplastic	50%
	Lymphoma	13%

Anaplastic thyroid cancer is a highly aggressive, locally invasive tumour. It typically presents in older patients with a rapidly increasing mass or lymph node. Anaplastic tumours invades local surrounding tissues causing compression symptoms including: pain, shortness of breath and dysphagia. The aggression of the tumour often leads to lymphovascular invasion and subsequent bone and lung metastasis. The cancer originates from follicular cells, which are poorly differentiated and have a high mitotic rate. The prognosis is poor with a 5-year survival rate quoted between 7% and 14%. Treatment is usually palliative, with a combination of radiotherapy and chemotherapy.

Discuss (10) Improve

Next question

Thyroid cancer ★

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's thyroiditis

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	Usually contain a mixture of papillary and colloidal filled follicles Histologically tumour has papillary projections and pale empty nuclei Seldom encapsulated Lymph node metastasis predominate Haematogenous metastasis rare

Type	Notes
Follicular adenoma	- Usually present as a solitary thyroid nodule - Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	- May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. - Vascular invasion predominates - Multifocal disease raree
Medullary carcinoma	- C cells derived from neural crest and not thyroid tissue - Serum calcitonin levels often raised - Familial genetic disease accounts for up to 20% cases - Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.
Anaplastic carcinoma	- Most common in elderly females - Local invasion is a common feature - Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

Next question

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Question 305 of 414 ✓

A 48-year-old man presents to the endocrine clinic. He has been feeling tired and lethargic for several weeks, with intolerance of cold weather and weight gain. More recently, he has developed a headache which is worse at night.

His blood tests show the following:

Thyroid stimulating hormone (TSH)	0.2 mU/L	(0.5-5.5)
Free thyroxine (T4)	2.1 pmol/L	(9.0 - 18)
Prolactin	2 ng/mL	(2 - 18)
FSH	0 IU/L	(1-7)
LH	0 IU/L	(1-8)

What is the most likely underlying diagnosis?

Glioma	1%
Haemangioblastoma	1%
Hypothyroidism	5%
Pituitary adenoma	56%
Pituitary apoplexy	38%

Non-functioning pituitary tumours present with hypopituitarism and pressure effects

Important for me Less important

Pituitary adenomas are a type of brain tumour that commonly occurs in people aged 30-50. 15% are non-functioning, and thus present with hypopituitarism and mass effect symptoms, such as postural headache and visual loss.

Gliomas can present with headaches as above, but would not be expected to cause hypopituitarism.

Haemangioblastomas are vascular tumours commonly associated with Von Hippel Lindau syndrome. They usually occur in the cerebellum, and would not be expected to cause hypopituitarism.

Hypothyroidism is incorrect. While the levels of T4 are low, indicating reduced activity of the thyroid gland, the underlying diagnosis, in this case, is a pituitary adenoma. Hypothyroidism alone would not explain the reduced gonadotropins and borderline-low prolactin.

Pituitary apoplexy is commonly seen in the presence of a pituitary tumour and is caused by bleeding into or impaired blood supply of the pituitary, This generally presents with sudden onset headache, followed by symptoms of non-functioning pituitary. The lack of acuteness in this presentation makes this unlikely.

👍 👎 💬 Discuss (5) Improve

Next question

Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:
- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)
- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
    - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:
- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:
- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of
- medical therapy:
  - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
  - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas
  - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery
  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

PassMedicine

Question 306 of 414 ✕

A General Practitioner refers a 45-year-old female patient to the endocrinology department with hypercalcaemia and raised parathyroid hormone levels. Her blood tests are highly suggestive of primary hyperparathyroidism. Her past medical history includes type 2 diabetes, which is well controlled on metformin alone.

Which feature would be the strongest indication for referral of the patient for consideration of parathyroid surgery?

	Co-existing type 2 diabetes	6%
	Post menopausal patient	9%
🟥	Persistent hypercalcaemia over 4 years	50%
	Vitamin D deficiency	6%
🟩	Age of 45	30%

NICE guidelines clearly stipulate the circumstances under which parathyroidectomy should be considered in primary hyperparathyroidism. These are listed below:

- Age under 50 years.
- Adjusted serum calcium concentration that is 0.25 mmol/L or more above the upper end of the reference range.
- Estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2 although this threshold depends on other factors, such as age.
- Renal stones or presence of nephrocalcinosis on ultrasound or CT.
- Presence of osteoporosis or osteoporotic fracture.
- Symptomatic disease

From the potential answers offered, the patient's age under 50 is the only answer that meets the NICE criteria.

(Source: NICE guidelines, hyperparathyroidism - http://cks.nice.org.uk/hypercalcaemia)

👍 👎 Discuss (8) Improve

Next question

Primary hyperparathyroidism

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':
- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

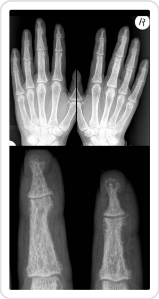
Associations
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations
- bloods
    - raised calcium, low phosphate
    - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan

- x-ray findings
    - pepperpot skull
    - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
    - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



Next question

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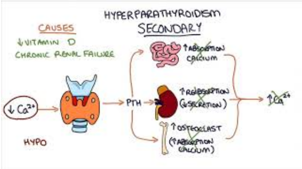
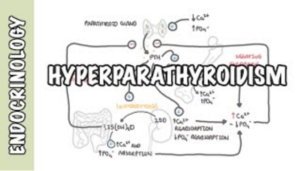

HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
HYPO
PTH
↑ABSORPTION CALCIUM
↑REABSORPTION (↓SECRETION)
↑OSTEOCLAST (↑ABSORPTION CALCIUM)
↑Ca2+

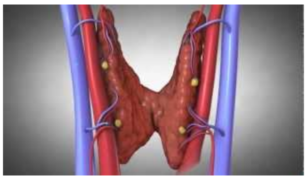
Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2



Parathyroid Glands and Hyperparathyroidism

Norman Parathyroid Center - YouTube 👍 20 👎 5

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Score: **23.9%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗

PassMedicine

Question 307 of 414 ✓

A 35-year-old female is referred to the endocrine clinic due to weight loss and palpitations. The following results are obtained:

TSH	< 0.05 mu/l
T4	178 mmol/l

Which one of the following features would most suggest a diagnosis of Grave's disease?

Atrial fibrillation	4%
Lid lag	31%
Family history of radioiodine treatment	3%
[✓ Pretibial myxoedema]	55%
Multinodular goitre	7%

Pretibial myxoedema is not seen in other causes of thyrotoxicosis and points towards a diagnosis of Graves'

Discuss (5) Improve

Next question

Graves' disease: features

Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis

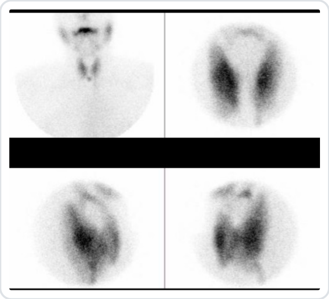
- eye signs (30% of patients)
  - exophthalmos
  - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
  - digital clubbing
  - soft tissue swelling of the hands and feet
  - periosteal new bone formation

Autoantibodies

- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

Thyroid scintigraphy

- diffuse, homogenous, increased uptake of radioactive iodine



Next question

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Question 308 of 414 ✓

You are reviewing a 24-year-old man who has recently been diagnosed with type 1 diabetes mellitus. He has no comorbidities and works as an accountant. What HbA1c target should he aim for initially?

42 mmol/mol	11%
45 mmol/mol	8%
48 mmol/mol	70%
50 mmol/mol	3%
52 mmol/mol	7%

In type 1 diabetics, a general HbA1c target of 48 mmol/mol (6.5%) should be used

Important for me Less important

The correct answer is **48 mmol/mol**. According to the National Institute for Health and Care Excellence (NICE) guidelines, an adult with type 1 diabetes mellitus should aim for a target HbA1c level of below 48 mmol/mol. This is because maintaining blood glucose levels as near to normal as possible reduces the risk of long-term microvascular complications, such as retinopathy, nephropathy, and neuropathy.

42 mmol/mol and **45 mmol/mol** are incorrect options. While these values are within the non-diabetic range, aiming for such low targets might increase the risk of hypoglycaemia, particularly in those with type 1 diabetes who are dependent on insulin injections. Hypoglycaemia can have serious consequences including confusion, loss of consciousness and seizures. Therefore, it's important that patients do not aim for overly aggressive targets which could put them at risk of hypoglycaemic episodes.

50 mmol/mol and **52 mmol/mol**, while not dangerously high, are above the recommended target according to NICE guidelines. Consistently elevated HbA1c levels increase the patient's risk of developing complications associated with diabetes. These include both microvascular complications like retinopathy, nephropathy and neuropathy; as well as macrovascular complications like heart disease and stroke.

Therefore, it is essential to balance the need for good glycaemic control (to prevent long-term complications) against the risks associated with hypoglycaemia when setting HbA1c targets. For this patient without comorbidities or specific individual considerations, an initial target of below 48 mmol/mol would be appropriate according to current UK guidelines.

👍 👎 Discuss (2) Improve

Next question

Diabetes mellitus: management of type 1 ★

The long-term management of type 1 diabetics is an important and complex process requiring the input of many different clinical specialties and members of the healthcare team. A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

NICE released guidelines on the diagnosis and management of type 1 diabetes in 2015. We've only highlighted a very select amount of the guidance here which will be useful for any clinician looking after a patient with type 1 diabetes.

HbA1c
- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

Self-monitoring of blood glucose
- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

Blood glucose targets
- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

Type of insulin

- offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

Metformin

- NICE recommend considering adding metformin if the BMI >= 25 kg/m^2

Next question

Textbooks

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Links

NICE 👍 4 👎 2

2015 Type 1 diabetes in adults: diagnosis and management

NICE 👍 3 👎 2

2015 Diabetes (type 1 and type 2) in children and young people

Report broken link

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Question 309 of 414 ✗

You are a trainee doctor on your emergency department rotation. You are asked to see a 34-year-old female patient as she has a raised early warning score.

She has presented due to increasing dizziness over the course of the last week. Additionally, she reports she has had a post-coital bleed which has continued since she had sexual intercourse 4 hours ago. She is feeling nauseous and looks pale when you approach her for assessment.

She admits that she has had several smaller post-coital bleeds over the last year. They occur every time she has been sexually active. She has had several sexual partners in her younger years and admits to not always using condoms. She is a smoker, casual drinker and admits to having gained weight over recent years. She also reports previous flares of genital herpes, but this isn't currently active.

Her observations are:

Blood pressure - 108/62 mmHg.
Heart rate - 104 beats per minute.
Respiratory rate - 21 breaths per minute.
Oxygen saturations - 95% on room air.
Temperature - 36.1°C.

On examination, she has active bleeding from her cervix which on flushing is of grossly abnormal appearance. She is referred urgently to gynaecology for suspected cervical cancer and management of the ongoing bleed.

In terms of risk, which of the following is likely to have contributed the most to the development of her underlying diagnosis?

🟥	Contraceptive implant use	3%
	Obesity	1%
🟩	Smoking	57%
	Herpes simplex virus 2 infection	4%
	Human papillomavirus 2 infection	35%

Women who smoke are at a two-fold increased risk of developing cervical cancer than women who do not

Important for me Less important

This question tests your knowledge of risk factors for cervical cancer. Smoking is known to double the risk of cervical cancer and is well established as a modifiable risk factor for the condition, as such it is the answer to this question.

Combined hormonal contraceptive use is associated with a reversible increase in the risk of cervical cancer. This is not the case with progesterone-only methods such as the contraceptive implant.

Obesity is a common risk factor for multiple cancers, but it doesn't contribute as great a risk as smoking. There is an increase in the risk of cervical cancer in obese patients, but this is believed to be partially due to barriers to the screening of these patients.

Herpes simplex virus (HSV) does not cause an increase in cervical cancer risk. Sexually transmitted infections can be commonly contracted together and increase the risk of contracting further infections. HSV itself does not increase cervical cancer risk, although, regular flares may be a sign of immunosuppression which does increase risk.

The human papillomavirus (HPV) is commonly implicated in cervical cancers. However, HPV 2 is the causative strain for palmar warts and is associated with minimal cervical cancer risk compared to smoking. It is essential to note that HPV 16 and 33 are much more carcinogenic than HPV 2, and they are included in vaccination programs and cervical cancer screening programs.

Discuss (3) Improve

Next question

Cervical cancer

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. It may be divided into:

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papillomavirus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov 10;370(9599):1609-21) confirmed the link

Next question

Textbooks

High-yield textbook

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Links

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Question 310 of 414 ✗

A 28-year-old woman is seen in the endocrine clinic with the results of the thyroid function tests shown below. For the preceding 2 weeks, she has been suffering from palpitations, excessive sweating and unintentional weight loss. On examination, she has a notable thyroid goitre, which is tender upon palpation.

Thyroid stimulating hormone (TSH)	9.4 mU/L	(0.5-5.5)
Free thyroxine (T4)	6.4 pmol/L	(9.0 - 18)

What is the most likely diagnosis?

	Follicular carcinoma	1%
	Grave's disease	9%
🟥	Hashimoto's disease	17%
	Papillary carcinoma	2%
🟩	Subacute (De Quervain's) thyroiditis	71%

Thyrotoxicosis with tender goitre = subacute (De Quervain's) thyroiditis

Important for me Less important

Subacute (De Quervain's thyroiditis) is an acute and painful swelling to the thyroid gland, likely preceded by a viral infection. There is an initial period of hyperthyroid, due to the release of thyroid hormone from damaged cells. Following the hyperthyroid state, a period of hypothyroid then ensues, eventually resolving back to a euthyroid state. The point that differentiates this diagnosis from the rest is a tender goitre, which is not anticipated in other causes of thyrotoxicosis.

Follicular carcinoma of the thyroid accounts for approximately 15% of thyroid carcinomas, more common in females, with the peak incidence in the 40-60 age bracket. Presentation is commonly an asymptomatic thyroid mass that is painless, and not associated with abnormal thyroid activity.

Grave's disease is a hyperthyroid state caused by autoimmune activation of TSH receptors. A goitre is usually present, but this would be painless on palpation. Associated proptosis and pretibial myxoedema can also present alongside the classic symptoms of thyrotoxicosis.

Hashimoto's disease, which is autoimmune-mediated thyroiditis, causes a hypothyroid state. A goitre can be present but would not be tender upon palpation.

Papillary carcinoma is the most common well-differentiated thyroid cancer. Presentation is typically an asymptomatic thyroid mass, sometimes associated with pressure symptoms on local structures. Derangement in thyroid function is not observed.

👍 👎 Discuss (1) Improve

Next question

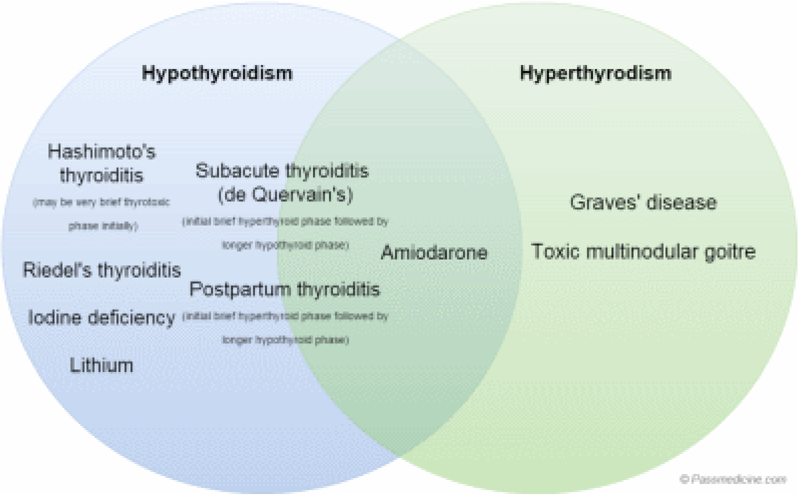
Subacute (De Quervain's) thyroiditis ★

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

Investigations
- thyroid scintigraphy: globally reduced uptake of iodine-131

Management
- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
Amiodarone
Graves' disease
Toxic multinodular goitre
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Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

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Score: **24.2%**

1 ✓
2 ✓
3 ✓
4 ✗

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Question 311 of 414 ✗

A neonate presents with failure to thrive and appears dehydrated.

Blood pressure is 65/35 mmHg, which is normal for her age.

Serum electrolytes show:

Sodium	127 mmol/L	(135 - 145 mmol/L
Potassium	2.1 mmol/L	(3.5 - 5.0 mmol/L)
Magnesium	0.89 mmol/L	(0.65 - 1.05 mmol/L)
Calcium	2.24 mmol/L	(2.00 - 2.70 mmol/L)
Chloride	88 mmol/L	(96 - 106 mmol/L)

Her venous blood gas shows a metabolic alkalosis. Urinary calcium is elevated.

Given the likely diagnosis, what is the most likely cause of this child's presentation?

	Decreased HCO3- reabsorption in proximal tubule	9%
	Defect in ENaC channel in distal convoluted tubule	6%
🟩	Defect in NKCC2 channel in ascending loop of Henle	65%
🟥	Defect in NaCl transporter in distal convoluted tubule	16%
	Inability to secrete H+ in distal convoluted tubule	4%

Bartter's syndrome results from a defective NKCC2 channel in the ascending loop of Henle

Important for me Less important

A **defective NKCC2 channel in the ascending loop of Henle** results in Bartter's syndrome. It presents in neonates with failure to thrive and salt wasting as seen here. It is often likened to giving large doses of furosemide. Tests show hypokalaemia, and hypochloraemic metabolic alkalosis, however, serum magnesium and calcium would be normal. Hypercalciuria is also often present, which helps distinguish it from Gitelman's syndrome (see below), where urinary calcium is often low.

A **defect in NaCl transporter in distal convoluted tubule** results in Gitelman's syndrome. Gitelman's syndrome tends to present later in childhood than Bartter's syndrome and is often seen as a 'less severe form'. Gitelman's syndrome will also cause a metabolic alkalosis and hypokalaemia but patients will often also have low serum calcium and magnesium and low urinary calcium, which is not the case here.

A **defect in ENaC channel in distal convoluted tubule** results in Liddle's syndrome and although this presents with hypokalaemia, will also cause hypertension. This patient is normotensive.

Inability to secrete H+ in distal convoluted tubule describes a type 1 renal tubule acidosis, although hypokalaemia would be present, this would show a metabolic alkalosis on the venous blood gas.

Decreased HCO3- reabsorption in proximal tubule describes a type 2 renal tubule acidosis, although hypokalaemia would be present, this would show a metabolic alkalosis on the venous blood gas.

👍 👎 Discuss (3) Improve

Next question

Bartter's syndrome ★

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na$^+$ K$^+$ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

> Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension

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Question 312 of 414

A mother is worried about her 13-month-old child as he has up to 12 wet nappies a day. Her sister had a kidney condition that she is worried might be affecting her child. On referral to a paediatrician, a suggestion of Bartter's syndrome is raised.

What is the underlying cause of this condition?

Mutated NKCC2 channel in the ascending loop of Henle	78%
Mutated NCl symporter in the distal convoluted tubule	12%
Mutated ADH receptors in the collecting duct	8%
Lack of ADH produced	2%
Absent insulin production	1%

Bartter's syndrome results from a defective NKCC2 channel in the ascending loop of Henle

Important for me Less important

Option 1 is correct. Bartter's syndrome is a rare inherited disorder due to mutated NKCC2 channels which presents with polydipsia, polyuria and a tendency to dehydration.

A mutated NCl symporter occurs in the closely associated condition, Gitelman syndrome.

Mutated ADH receptors and a lack of ADH production describe what occurs in nephrogenic and central diabetes insipidus respectively.

Absent insulin production occurs in type 1 diabetes mellitus.

Discuss (1) Improve

Next question

Bartter's syndrome

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na$^+$ K$^+$ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

> Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features

- usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

Next question

Textbooks

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Links

Royal College of Physicians 👍 9 👎 3

2012 Renal tubular disorders review

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Question 313 of 414 ✓

A 73-year-old man is seen in incontinence clinic by a speciality doctor. He has a past medical history of urge incontinence. He has tried oxybutynin in the past but did not find it helpful. He didn't tolerate tolterodine either due to his longstanding constipation. The doctor prescribes a 6-week course of mirabegron.

What is the mechanism of action of mirabegron?

Beta-2 agonist	10%
Beta-1 agonist	4%
Beta-3 agonist	60%
Alpha-1 agonist	13%
Alpha-1 antagonist	13%

Mirabegron is a beta-3 agonist

Important for me Less important

Mirabegron is a beta-3 agonist used in the management of urge incontinence if the other drugs such as oxybutynin fail to work or are contraindicated.

Salbutamol is a beta-2 receptor agonist and causes bronchial smooth muscle relaxation. Beta-2 receptors are predominantly found in the lungs.

Beta-1 agonists, such as dobutamine, are used as inotropic agents in congestive heart failure.

Doxazosin is an alpha-1 antagonist, used in the management of hypertension.

Phenylephrine is an alpha-1 agonist. It acts as a vasoconstrictor and is used as a nasal decongestant.

👍 👎 Discuss (1) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification

- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line

  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

High-yield textbook

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Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

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Question 314 of 414 ✗

A 45-year-old female is admitted to the Emergency Department with abdominal pain associated with vomiting. She has a past medical history of hypothyroidism and takes thyroxine. On examination she is pyrexial at 37.6°C. Pulse is 110 bpm with a blood pressure of 100/64 mmHg. Blood results show the following:

Na^+	131 mmol/l
K^+	4.9 mmol/l
Urea	8.1 mmol/l
Creatinine	110 µmol/l
Glucose	3.3 mmol/l

What treatment should be given first?

Ceftriaxone + benzylpenicillin	2%
Glucagon	24%
🟥 Propranolol	12%
Triiodothyronine	3%
🟩 Hydrocortisone	60%

This is a typical history of Addison's. Patients may have a history of other autoimmune conditions such as thyroid disorders. Steroids should be given as soon as possible

Discuss (12) Improve

Next question

Addison's disease ★

Autoimmune destruction of the adrenal glands is the most common cause of primary hypoadrenalism in the UK, accounting for 80% of cases. This is termed Addison's disease and results in reduced cortisol and aldosterone being produced.

Features

- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases)
    - ACTH is derived from a larger precursor molecule called proopiomelanocortin (POMC). When POMC is cleaved to produce ACTH, other melanocyte-stimulating hormones (MSH) are also produced. These MSHs have the effect of stimulating melanocytes in the skin to produce more melanin, the pigment responsible for skin colour
    - primary Addison's is associated with hyperpigmentation whereas secondary adrenal insufficiency is not
- vitiligo
- loss of pubic hair in women
- hypotension
- hypoglycaemia
- hyponatraemia and hyperkalaemia may be seen
- crisis: collapse, shock, pyrexia

Other causes of hypoadrenalism

Primary causes

- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

Secondary causes

- pituitary disorders (e.g. tumours, irradiation, infiltration)

Exogenous glucocorticoid therapy

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 2 👎 0

Addison's disease

Royal College of Physicians 👍 4 👎 2

2017 Adrenal insufficiency â€″ recognition and management

Report broken link

Media

ADDISON'S DISEASE

Addison's disease

Armando Hasudungan - YouTube 👍 30 👎 2

Primary adrenal insufficiency (Addison's disease)

Osmosis - YouTube 👍 13 👎 5

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← Question 315 of 414 ✗ →

A 73-year-old female present with urge incontinence having a significant impact on her quality of life. She has undergone supervised bladder training with no improvement in symptoms and is keen to trial medication. She has a past medical history of atrial fibrillation, well-controlled hypertension and recurrent urinary retention.

What would be the most appropriate first-line treatment?

🟩	Mirabegron	61%
	Oxybutynin	23%
	Pelvic floor exercises	7%
🟥	Tolterodine	6%
	Surgical repair	2%

Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative

Important for me Less important

The key to this question is to recognise that antimuscarinics the usual treatment for urge incontinence are contraindicated in patients with a history of urinary retention. As such mirabegron is the correct answer.

Oxybutynin is an antimuscarinic and would be contraindicated in this patient.

Pelvic floor exercises are used in the treatment of stress incontinence and are unlikely to have an effect in patients with pure urge incontinence.

Tolterodine is also an antimuscarinic and should not be used in a history of urinary retention.

Surgical repair would be used in patients with stress incontinence that has not improved with pelvic floor exercises and as such is not the correct answer.

👍 👎 Discuss (9) Improve

Next question

Urinary incontinence

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification

- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
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- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

Textbooks

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NICE 👍 5 👎 6

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← Question 316 of 414 ✗ →

A 70-year-old woman presents to her GP with a swelling in the front of her neck. She has noticed a lump that has become gradually bigger over the last 2 months. She has a past medical history of hypothyroidism, for which she has taken levothyroxine since diagnosis.

On examination, she has a solitary, painless, hard, immobile nodule at the front of her neck. The nodule does not move on tongue protrusion.

What is the most likely cause of the swelling?

	De Quervain's thyroiditis	4%
	Papillary thyroid cancer	20%
	Riedel's thyroiditis	24%
🟥	Thyroglossal cyst	7%
🟩	Thyroid lymphoma	45%

Hashimoto's thyroiditis is associated with thyroid lymphoma

Important for me Less important

Thyroid lymphoma is correct. The description of the mass as a solitary, painless, hard, immobile nodule is compatible with a malignancy. The patient has a background of hypothyroidism, the most common cause of which is Hashimoto's thyroiditis. Hashimoto's thyroiditis is associated with the development of thyroid lymphoma.

De Quervain's thyroiditis is incorrect. This would be more likely to produce a transient hyperthyroid state, followed by a hypothyroid state. It commonly occurs secondary to a viral infection, and it would produce a diffuse, tender goitre. This is not seen here.

Papillary thyroid cancer is incorrect. The story here is of a rapidly growing thyroid mass in a patient with likely Hashimoto's thyroiditis. Papillary thyroid cancer is a more slow-growing form of thyroid cancer. Although more common than thyroid lymphoma, it is usually seen in a younger demographic and is not associated with Hashimoto's thyroiditis.

Riedel's thyroiditis is incorrect. This is characterised by inflammation of the thyroid gland, following which normal thyroid tissue is replaced by fibrous tissue. This leaves a hard, woody goitre on palpation. This is not seen here, and so this answer is incorrect.

Thyroglossal cyst is incorrect. Although the description of a solitary lesion would match this, the lesion may be described as cystic/mobile. It would also move upwards on tongue protrusion, but the lesion described in this case is immobile and does not move on tongue protrusion.

👍 👎 Discuss (5) Improve

Next question

Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's thyroiditis

Management of papillary and follicular cancer
- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	- Usually contain a mixture of papillary and colloidal filled follicles - Histologically tumour has papillary projections and pale empty nuclei - Seldom encapsulated - Lymph node metastasis predominate - Haematogenous metastasis rare
Follicular adenoma	- Usually present as a solitary thyroid nodule - Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	- May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. - Vascular invasion predominates - Multifocal disease raree
Medullary carcinoma	- C cells derived from neural crest and not thyroid tissue - Serum calcitonin levels often raised - Familial genetic disease accounts for up to 20% cases - Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.
Anaplastic carcinoma	- Most common in elderly females - Local invasion is a common feature - Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

Next question

Textbooks

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Links

British Thyroid Association 👍 3 👎 3

2014 Guidelines for the Management of Thyroid Cancer

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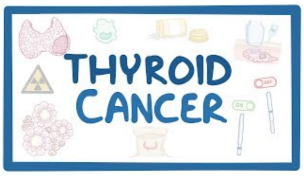
Media



Thyroid cancer

Osmosis - YouTube 👍 20 👎 1

Thyroid Nodule

Armando Hasudungan - YouTube 👍 12 👎 4

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Score: **24.1%**

1 ✓
2 ✓
3 ✓
4 ✗

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← Question 317 of 414 ✕ ⚐ →

A 48-year-old lady is seen in the diabetes clinic with uncontrolled blood sugars ranging from 14 mmol/L to 22 mmol/L. She has a past medical history of type 2 diabetes, ischaemic heart disease, rheumatoid arthritis and recurrent episodes of thrush alongside chronic obstructive pulmonary disease. Her body mass index is 30. Which medical co-morbidity is the strongest contraindication to starting an SGLT2 (sodium glucose transport protein 2) inhibitor class of drugs?

	Ischaemic heart disease	20%
🟥	Chronic obstructive pulmonary disease	6%
	Type 2 diabetes	3%
	Rheumatoid arthritis	6%
🟩	Recurrent thrush	66%

Dapagliflozin is a newer drug for the treatment of diabetes. It is a member of the sodium-glucose transport protein 2 (SGLT2) inhibitor class of drugs.

SGLT2 inhibitors prevent the resorption of glucose from the proximal renal tubule, resulting in more glucose being secreted in the urine. Due to an increased amount of glucose being secreted in the urine, these medications are contra-indicated in patients with recurrent thrush. The increased amount of glucose in the urine is thought to predispose to bacterial growth. It should also be noted that urine dip sticks will test positive for glucose.

The other medications in this class include: canagliflozin & empagliflozin

The other answers are distractors with no known contraindication to SGLT2 inhibitor use in ischaemic heart disease, chronic obstructive pulmonary disease or rheumatoid arthritis. SGLT2's are indicated in patients with type 2 diabetes. Note that although trials are ongoing, SGLT2 inhibitors are not currently licensed as an adjunct in patients with type 1 diabetes.

👍 👎 Discuss (7) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

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BNF 👍 3 👎 9

Dapagliflozin

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Question 318 of 414 ✗

A woman presents to the emergency department with confusion. She is found to be hypothermic with a low blood pressure and bradycardia. After further examination and investigation, she is found to be in a myxoedemic coma.

What is the most appropriate first-line treatment for this lady's presentation?

	Adrenaline and levothyroxine	9%
🟥	Prednisolone and levothyroxine	6%
🟩	Hydrocortisone and levothyroxine	71%
	Hydrocortisone and fludrocortisone	6%
	Adrenaline and hydrocortisone	8%

Myxoedemic coma is treated with thyroxine and hydrocortisone

Important for me Less important

This question is asking about a woman presenting with confusion, bradycardia, hypotension who has been diagnosed with a myxoedemic coma. It is asking for the first initial treatment, thus the correct answer is hydrocortisone and levothyroxine.

Levothyroxine is used to replace the low levels of thyroid hormone causing the patient's symptoms.

Hydrocortisone is given to treat adrenal insufficiency. Patients suffering from a myxoedemic coma due to secondary hypothyroidism are at risk of hypopituitarism due to the location of the lesion. Thus patients are treated as presumed adrenal insufficiency until it has been ruled out.

Discuss (7) Improve

Next question

Hypothyroidism: features ★

General

- Weight gain
- Lethargy
- Cold intolerance

Skin

- Dry (anhydrosis), cold, yellowish skin
- Non-pitting oedema (e.g. hands, face)
- Dry, coarse scalp hair, loss of lateral aspect of eyebrows

Gastrointestinal

- Constipation

Gynaecological

- Menorrhagia

Neurological

- Decreased deep tendon reflexes
- Carpal tunnel syndrome

A hoarse voice is also occasionally noted.

Next question

Textbooks

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Question 319 of 414 ✗

Which one of the following features is least commonly seen in Gitelman's syndrome?

	Hypokalaemia	8%
🟩	Hypertension	61%
🟥	Metabolic alkalosis	10%
	Hypocalciuria	15%
	Hypomagnesaemia	7%

Gitelman's syndrome: normotension, hypokalaemia + hypocalciuria

Important for me Less important

The correct answer is **Hypertension**. Gitelman's syndrome is a renal tubular disorder characterised by hypokalaemia, metabolic alkalosis, hypocalciuria and hypomagnesaemia. Hypertension, however, is rarely seen in this condition.

Hypokalaemia is incorrect as it is a common feature of Gitelman's syndrome. The condition results from mutations in the SLC12A3 gene which encodes the thiazide-sensitive Na-Cl cotransporter (NCCT) in the distal convoluted tubule. This leads to impaired sodium reabsorption causing increased sodium delivery to the collecting ducts where sodium reabsorption in exchange for potassium and hydrogen ions takes place. This leads to excessive loss of potassium (hypokalaemia) and hydrogen ions (resulting in metabolic alkalosis).

Metabolic alkalosis is also incorrect as it is commonly seen in Gitelman's syndrome. As mentioned earlier, impaired reabsorption of sodium causes increased exchange for hydrogen ions leading to their excessive loss and resulting in metabolic alkalosis.

Hypocalciuria or low urinary calcium levels are also typically seen in patients with Gitelman's syndrome making this option incorrect too. The exact mechanism isn't fully understood but it's thought that increased sodium delivery to the collecting ducts enhances calcium reabsorption.

Lastly, **Hypomagnesaemia**, or decreased serum magnesium levels, is another hallmark of Gitelman's syndrome making this option incorrect as well. Impaired function of NCCT due to mutations in SLC12A3 gene not only affects sodium reabsorption but also magnesium absorption leading to its increased urinary loss and consequent hypomagnesaemia.

👍 👎 Discuss (5) Improve

Next question

Gitelman's syndrome ★

Gitelman's syndrome is due to a defect in the thiazide-sensitive Na^+ Cl- transporter in the distal convoluted tubule.

Features
- normotension
- hypokalaemia
- hypocalciuria
- hypomagnesaemia
- metabolic alkalosis

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **23.8%**

PassMedicine

Question 320 of 414 ✗

A 41-year-old woman is investigated for hot flushes and night sweats. Bloods show a significantly raised FSH level and her symptoms are attributed to the menopause. Following discussions with the patient she elects to have hormone replacement treatment. What is the most significant risk of prescribing an oestrogen-only preparation rather than a combined oestrogen-progestogen preparation?

	Increased risk of venous thromboembolism	19%
	Increased risk of ovarian cancer	5%
🟩	Increased risk of endometrial cancer	55%
	Increased risk of breast cancer	20%
🟥	Increased risk of colorectal cancer	1%

HRT: unopposed oestrogen increases risk of endometrial cancer

Important for me Less important

The most significant risk of prescribing an oestrogen-only preparation rather than a combined oestrogen-progestogen preparation is the **increased risk of endometrial cancer**. Oestrogen stimulates the growth of the endometrium, and without the balancing effect of progestogen, there is an increased risk of unopposed endometrial proliferation, which can lead to hyperplasia and eventually endometrial cancer. Combined preparations containing both oestrogen and progestogen help to counteract this risk by providing a more balanced hormonal environment.

An **increased risk of venous thromboembolism** is a known side effect of hormone replacement therapy (HRT), but this is not specific to oestrogen-only preparations. Both oestrogen-only and combined preparations have been associated with an increased risk of venous thromboembolism, with the risk being higher in those with additional predisposing factors such as obesity or a history of previous thromboembolic events.

An **increased risk of ovarian cancer** has been suggested in some studies involving HRT use, but the overall evidence remains inconclusive. Furthermore, this potential increased risk does not seem to be limited to oestrogen-only preparations; it may also apply to combined preparations.

Regarding an **increased risk of breast cancer**, studies have shown that long-term use of combined HRT has a higher association with breast cancer compared to oestrogen-only HRT. Therefore, using an oestrogen-only preparation would not increase the risk compared to a combined preparation; in fact, it might be slightly lower.

Finally, an **increased risk of colorectal cancer** is not associated with either oestrogen-only or combined HRT. Some studies have even suggested that HRT use might be associated with a reduced incidence of colorectal cancer, although this remains an area of ongoing research.

👍 👎 Discuss (5) Improve

Next question

Hormone replacement therapy: adverse effects

Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen (combined with a progestogen in women with a uterus) to help alleviate menopausal symptoms.

Side-effects
- nausea
- breast tenderness
- fluid retention and weight gain

Potential complications
- increased risk of breast cancer
    - increased by the addition of a progestogen
    - in the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
    - the increased risk relates to the duration of use
    - the risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT
- increased risk of endometrial cancer
    - oestrogen by itself should not be given as HRT to women with a womb
    - reduced by the addition of a progestogen but not eliminated completely
    - the BNF states that the additional risk is eliminated if a progestogen is given continuously
- increased risk of venous thromboembolism
    - increased by the addition of a progestogen
    - transdermal HRT does not appear to increase the risk of VTE

  - NICE state women requesting HRT who are at high risk for VTE should be referred to haematology before starting any treatment (even transdermal)
- increased risk of stroke
- increased risk of ischaemic heart disease if taken more than 10 years after menopause

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 4 👎 0

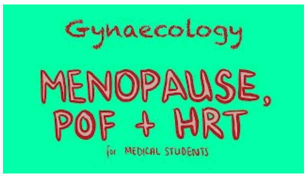
2015 Menopause guidelines

The British Menopause Society and Women's Health Concern 👍 1 👎 2

Recommendations on hormone replacement therapy

Report broken link

Media



Menopause

MedFlix - YouTube 👍 7 👎 2

PassMedicine

← Question 321 of 414 ✗ →

A 48-year-old male presents to the clinic. He complains of excessive flatulence following starting a new agent for management of his type 2 diabetes mellitus. He has no other past medical history.

What drug is most likely implicated?

	Metformin	46%
	Gliclazide	3%
🟩	Acarbose	45%
🟥	Sitagliptin	4%
	Empagliflozin	2%

Excessive flatulence is an extremely common side effect of acarbose which is often poorly tolerated

Important for me Less important

Acarbose is an inhibitor of intestinal alpha glucosidases, which results in decreased absorption of starch and sucrose. Since acarbose prevents the degradation and absorption of complex carbohydrates into glucose, an increased carbohydrate load will be delivered to the colon. In the colon, bacteria digest the complex carbohydrates, causing gastrointestinal side-effects such as flatulence and diarrhoea. Excessive flatulence is the most commonly reported side effect and is often the reason for discontinuation of the drug.

Metformin can also cause gastrointestinal side effects, however it is often diarrhoea rather than excessive flatulence, making acarbose the better answer.

Gliclazide is a sulphonylurea agent. The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. Side effects include hypoglycaemia, cholestatic jaundice and diarrhoea.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. Side effects include peripheral oedema and diarrhoea.

Empagliflozin is an inhibitor of the sodium glucose co-transporter-2 (SGLT-2). It cause increased glucose excretion in the urine which predisposed to recurrent urinary tract infections.

👍 👎 Discuss (3) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015
- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

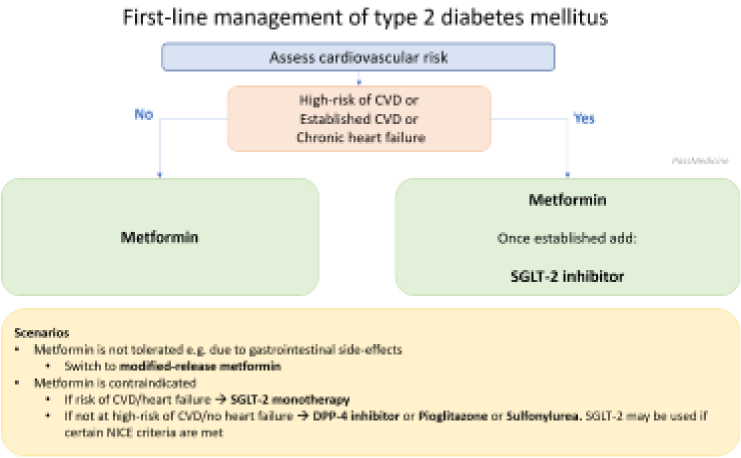
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	**HbA1c target**
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios

- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

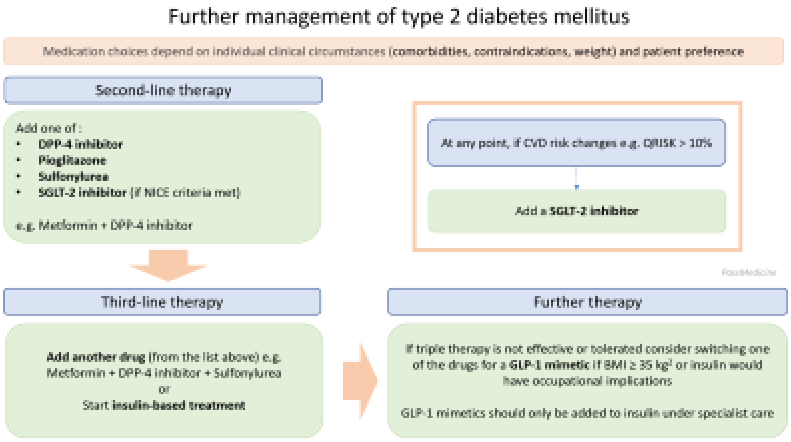
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
    - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
    - the patient has established CVD
    - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
    - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
    - DPP-4 inhibitor or pioglitazone or a sulfonylurea
    - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:
- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:
- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

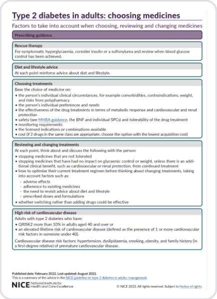
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:
- BMI ≥ 35 kg/m² and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin
- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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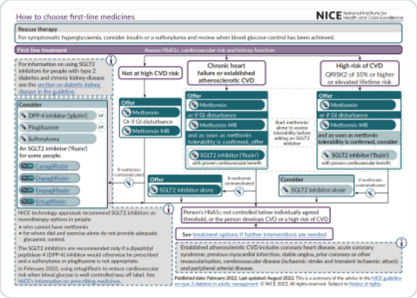

How to choose first-line medicines

NICE National Institute for Health and Care Excellence
Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.
First-line treatment
Assess HbA1c, cardiovascular risk and kidney function
For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.
Consider
DPP-4 inhibitor ('gliptin')
or
Pioglitazone
or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR
If metformin contraindicated
Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin')
with proven cardiovascular benefit
Start metformin alone to assess tolerability before adding an SGLT2 inhibitor
High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin')
with proven cardiovascular benefit
Offer
SGLT2 inhibitor alone
If metformin contraindicated
Consider
SGLT2 inhibitor alone
If metformin contraindicated
Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD
See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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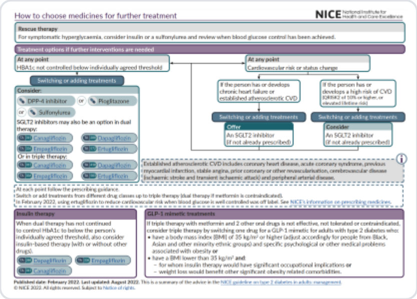

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence
Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.
Treatment options if further interventions are needed
At any point
HBA1c not controlled below individually agreed threshold
Switching or adding treatments
Consider:
DPP-4 inhibitor
or
Pioglitazone
or
Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Or in triple therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
At any point
Cardiovascular risk or status change
If the person has or develops chronic heart failure or established atherosclerotic CVD
If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m² or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m² **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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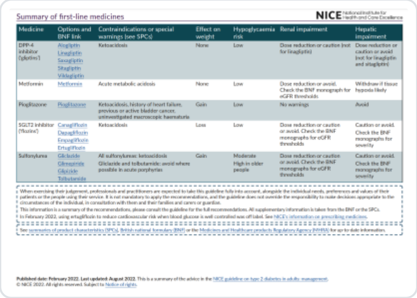

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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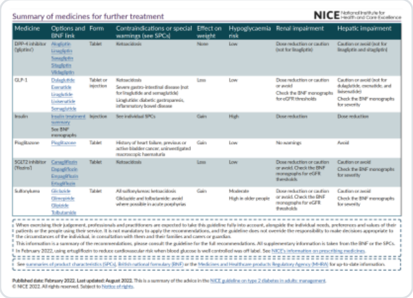

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

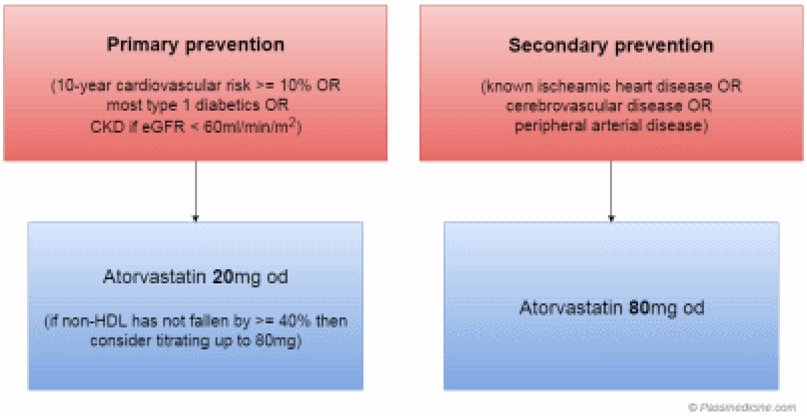
	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischaemic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

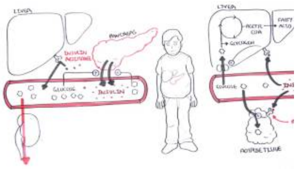
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

PassMedicine

Question 322 of 414 ✗

An 24-year-old woman is reviewed due to facial hirsutism. You suspect a diagnosis of polycystic ovarian syndrome (PCOS). Which one of the following features would suggest the need for further investigations before confidently making a diagnosis of PCOS?

🟩 Clitoromegaly	45%
🟥 Acanthosis nigricans	13%
Obesity	7%
Amenorrhoea	30%
Acne	4%

Clitoromegaly is seen occasionally in PCOS but is normally associated with very high androgen levels. If clitoromegaly is found then further investigations to exclude an ovarian or adrenal androgen secreting tumour are required.

Discuss (8) Improve

Next question

Polycystic ovarian syndrome: features and investigation ★

Polycystic ovary syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. The aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

Features
- subfertility and infertility
- menstrual disturbances: oligomenorrhoea and amenorrhoea
- hirsutism, acne (due to hyperandrogenism)
- obesity

- acanthosis nigricans (due to insulin resistance)

Investigations

- pelvic ultrasound: multiple cysts on the ovaries
- NICE Clinical Knowledge Summaries recommend the following baseline investigatons: FSH, LH, prolactin, TSH, testosterone, sex hormone-binding globulin (SHBG) are useful investigations
    - raised LH:FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis
    - prolactin may be normal or mildly elevated
    - testosterone may be normal or mildly elevated - however, if markedly raised consider other causes
    - SHBG is normal to low in women with PCOS
- check for impaired glucose tolerance

Diagnostic criteria

- a formal diagnosis should only be made after performing investigations to exclude other conditions
- the Rotterdam criteria state that a diagnosis of PCOS can be made if 2 of the following 3 are present:
    - infrequent or no ovulation (usually manifested as infrequent or no menstruation)
    - clinical and/or biochemical signs of hyperandrogenism (such as hirsutism, acne, or elevated levels of total or free testosterone)
    - polycystic ovaries on ultrasound scan (defined as the presence of ≥ 12 follicles (measuring 2-9 mm in diameter) in one or both ovaries and/or increased ovarian volume > 10 cm^3)

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Obstetricians and Gynaecologists 👍 2 👎 0

2014 Long-term Consequences of Polycystic Ovary Syndrome

Clinical Knowledge Summaries 👍 2 👎 0

Polycystic ovarian syndrome

Patient.info 👍 2 👎 1

Polycystic ovarian syndrome review

Report broken link

Score: **23.6%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗
12 ✓
13 ✗
14 ✓
15 ✗

PassMedicine

Question 323 of 414 ✗

A 40-year-old woman complains of feeling tired all the time and putting on weight. On examination a diffuse, non-tender goitre is noted. Blood tests are ordered:

TSH	15.1 mU/l
Free T4	7.1 pmol/l
ESR	14 mm/hr
Anti-TSH receptor stimulating antibodies	Negative
Anti-thyroid peroxidase antibodies	Positive

What is the most likely diagnosis?

	Pituitary failure	1%
🟥	Primary atrophic hypothyroidism	2%
	De Quervain's thyroiditis	4%
🟩	Hashimoto's thyroiditis	84%
	Grave's disease	9%

Hashimoto's thyroiditis = hypothyroidism + goitre + anti-TPO

Important for me Less important

This patient has Hashimoto's thyroiditis, as evidenced by the hypothyroidism, goitre and anti-thyroid peroxidase antibodies. De Quervain's thyroiditis typically causes a painful goitre and a raised ESR. Around 90% of patients with Grave's disease have anti-TSH receptor stimulating antibodies.

Discuss (3) Improve

Next question

Hashimoto's thyroiditis

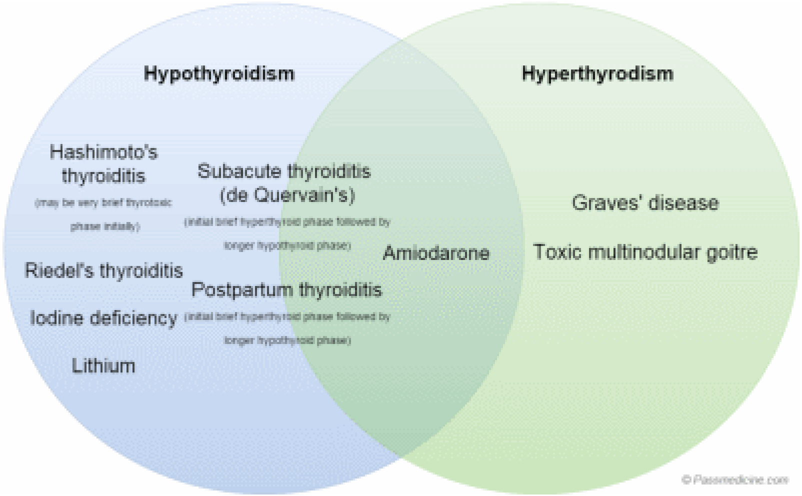
Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features

- features of hypothyroidism
- goitre: firm, non-tender
- anti-thyroid peroxidase (TPO) and also anti-thyroglobulin (Tg) antibodies

Associations

- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of MALT lymphoma


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Graves' disease
Toxic multinodular goitre
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

PassMedicine

← Question 324 of 414 ✗ ⚐ →

A 32-year-old woman presents to her general practitioner with reports of debilitating fatigue. She is 13 weeks pregnant with her first child. The pregnancy has been uncomplicated thus far. She has no significant past medical history.

The examination is unremarkable.

Blood tests:

Free T4	14 pmol/L	(12 - 22)
Total T4	15 mcg/dl	(5-12)
Free T3	3.4 pmol/L	(3.1 - 6.8)
Total T3	5.4 nmol/L	(0.9-2.8)
TSH	0.4 mU/L	(0.2-2.5)

What is the correct interpretation of her blood test results?

🟩	Normal result in pregnancy	73%
	Sick euthyroid	6%
	Subclinical hyperthyroidism	12%
🟥	Subclinical hypothyroidism	6%
	Thyroiditis	3%

Raised total T3 and T4 but normal fT3 and fT4 suggest high concentrations of thyroid binding globulin, which can be seen during pregnancy

Important for me Less important

Normal result in pregnancy is the correct answer. Raised total T3 and T4 but normal fT3 and fT4 suggest high concentrations of thyroid-binding globulin, which can be seen during pregnancy. Fatigue is a common symptom in pregnancy itself and does not necessarily need an alternative explanation.

Sick euthyroid is incorrect. In this state (i.e. during an intercurrent severe illness) we would expect low levels of free T4, free T3 and TSH.

Subclinical hyperthyroidism is incorrect. This would be suggested by a low TSH and a normal free T4 level.

Subclinical hypothyroidism is incorrect. This would be suggested by a high TSH level and normal free T4 level.

Thyroiditis is incorrect. This may cause the patient to be biochemically hyperthyroid with a suppressed TSH (absent here). Thyroiditis is more common in post-partum patients rather than during pregnancy.

Discuss Improve

Next question

Pregnancy: thyroid problems

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

Thyrotoxicosis

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management
- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: '*Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole*'

- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

Hypothyroidism

Key points

- thyroxine is safe during pregnancy
- serum thyroid-stimulating hormone measured in each trimester and 6-8 weeks post-partum
- women require an increased dose of thyroxine during pregnancy
    - by up to 50% as early as 4-6 weeks of pregnancy
- breastfeeding is safe whilst on thyroxine

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Clinical Knowledge Summaries 👍 15 👎 9

Management of hypothyroidism in pregnancy

Report broken link

PassMedicine

Question 325 of 414 ✗

A 35-year-old patient is referred to the medical assessment unit. He reported excessive sweating to his GP and was found to be very hypertensive (182/101 mmHg) at the initial assessment. He has a past medical history of medullary thyroid cancer, which was surgically treated. He is on levothyroxine.

On examination, the patient is tall (2.04m) with a high arched-palate. He is flushed.

Blood tests:

Hb	138 g/L	Male: (135-180) Female: (115 - 160)
Platelets	189 * 10^9/L	(150 - 400)
WBC	4.2 * 10^9/L	(4.0 - 11.0)
Na^+	136 mmol/L	(135 - 145)
K^+	4.2 mmol/L	(3.5 - 5.0)
Urea	5.1 mmol/L	(2.0 - 7.0)
Creatinine	88 µmol/L	(55 - 120)
CRP	4 mg/L	(< 5)
Plasma metanephrines	1400 pmol/L	(<510)
TSH	1.2 mIU/L	(0.5 to 5.0)
PTH	32 pg/ml	(14 - 65)
Calcium	2.21 mmol/L	(2.20-2/60)

What is the unifying diagnosis?

🟥	Multiple endocrine neoplasia type I	9%
	Multiple endocrine neoplasia type IIa	26%
🟩	Multiple endocrine neoplasia type IIb	62%
	Neurofibromatosis type I	1%

Von Hippel-Lindau disease 3%

Medullary thyroid cancer, phaeochromocytoma, marfanoid body habitus - multiple endocrine neoplasia type IIb

Important for me Less important

Multiple endocrine neoplasia type IIb is correct. The patient has a past history of medullary thyroid cancer. Additionally, they have marfanoid body habitus (tall with high arched palate) and symptoms and signs suggestive of a phaeochromocytoma (flushing, hypertension, raised plasma metanephrines). Taken together, this constellation of pathologies suggests multiple endocrine neoplasia type IIb.

Multiple endocrine neoplasia type IIa is incorrect. While medullary thyroid cancer and phaeochromocytoma are features of this disorder, it is not associated with marfanoid body habitus. Additionally, it is associated with hyperparathyroidism, which is absent.

Multiple endocrine neoplasia type I is incorrect. Hyperparathyroidism is the central feature of this condition, which is absent in this case.

Neurofibromatosis type I is incorrect. This is associated with phaeochromocytoma and hypertension. However, the characteristic skin findings of this condition are absent i.e. cafe au lait spots and neurofibromas.

Marfan's syndrome is incorrect. While this patient does have a marfanoid body habitus, Marfan's syndrome alone would not explain the other findings of medullary thyroid cancer and a phaeochromocytoma.

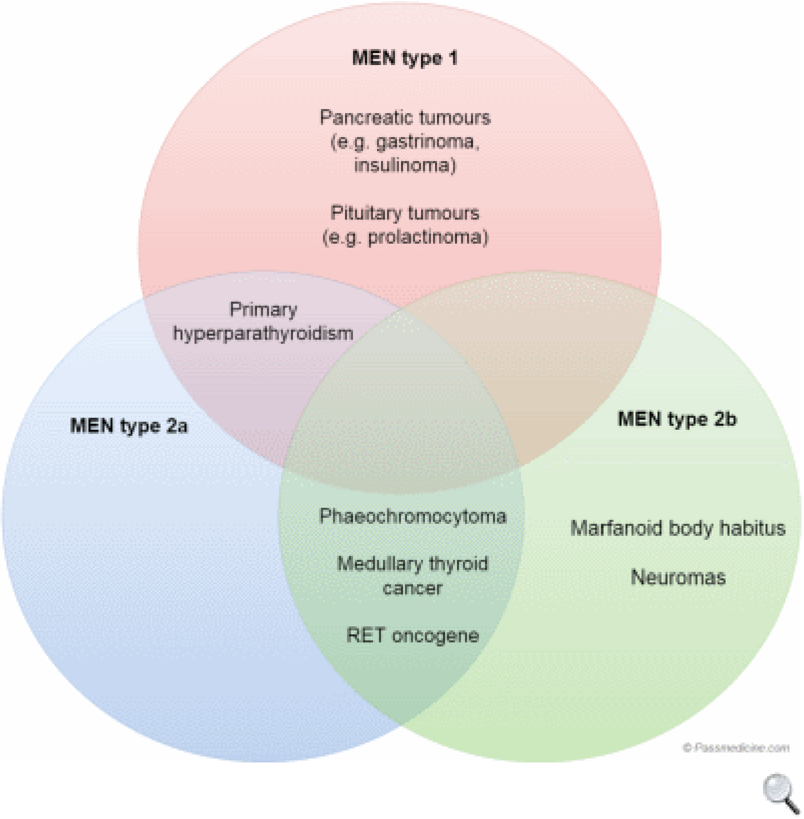
Discuss (3) Improve

Next question

Multiple endocrine neoplasia

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	Medullary thyroid cancer 1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
© Passmedicine.com

Venn diagram showing the different types of MEN and their associated features

Next question

Question 326 of 414 ✕

A 25-year-old female has type I diabetes. Her HbA1c is 58 mmol/L. Her blood pressure is 126/68 mmHg. Her BMI is 28 kg/m^2. She is using a basal-bolus regimen which she finds easy to manage. She is not keen to increase her total insulin dose. Which of the following adjuncts could you consider to help improve her glycaemic control?

🟩	Add metformin	63%
	Switch to a mixed insulin regime	9%
	Add sitagliptin	6%
🟥	Add exenatide	9%
	Enrol in supported weight loss programme	13%

Patients with type I diabetes and a BMI > 25 should be considered for metformin in addition to insulin

Important for me Less important

The correct answer is to add metformin. NICE recommends that adding metformin should be considered in type I diabetics with a BMI > 25, either on patient preference or to avoid the need to increase their insulin therapy. The other oral diabetic medications are not currently recommended. Weight loss is likely to be beneficial but there is greater evidence for benefit with the use of metformin. A mixed insulin regime might be used if a multiple injection basal-bolus regime was not suited to the patient's lifestyle but is not usually chosen for better glycaemic control.

NICE: Type I diabetes in adults
https://www.nice.org.uk/guidance/ng17/chapter/1-recommendations

Discuss (4) Improve

Next question

Diabetes mellitus: management of type 1 ★

The long-term management of type 1 diabetics is an important and complex process requiring the input of many different clinical specialties and members of the healthcare team. A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

NICE released guidelines on the diagnosis and management of type 1 diabetes in 2015. We've only highlighted a very select amount of the guidance here which will be useful for any clinician looking after a patient with type 1 diabetes.

HbA1c
- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

Self-monitoring of blood glucose
- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

Blood glucose targets
- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

Type of insulin
- offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

Metformin
- NICE recommend considering adding metformin if the BMI >= 25 kg/m^2

Next question

PassMedicine

Question 327 of 414 ✗

A 46-year-old man was diagnosed with type II diabetes mellitus. Despite perseverance, he was unable to tolerate metformin therapy. A decision is made to commence him on alogliptin.

What is the mechanism of action of this drug?

	Directly stimulates the release of insulin from pancreatic beta cells	6%
	Increases production of glucagon-like-peptide-1	18%
🟥	Inhibits the SGLT2 receptor	8%
🟩	Reduce the peripheral breakdown of incretins	66%
	Reduces insulin resistance	3%

Gliptins (DPP-4 inhibitors) reduce the peripheral breakdown of incretins such as GLP-1

Important for me Less important

Reduces the peripheral breakdown of incretins is correct. The incretin hormones (i.e. glucagon-like-peptide-1) are involved in the regulation of glucose homeostasis. These hormones are rapidly degraded by the enzyme DPP-4. Gliptins (e.g. alogliptin) inhibit DPP-4, which leads to a glucose-dependent increase in insulin secretion and a reduction in glucagon secretion.

Increases production of glucagon-like-peptide-1 is incorrect. Gliptins work by inhibiting DPP-4, which exerts its pharmacological effect by reducing the breakdown of incretin hormones (i.e. GLP-1). It does not work by increasing the production of GLP-1.

Directly stimulates the release of insulin from pancreatic beta cells is incorrect. This is the mechanism of sulfonylureas (e.g. gliclazide). Due to their mechanism, sulfonylureas are associated with weight gain and increase the risk of hypoglycaemia. They are only effective in patients with residual beta-cell function.

Inhibits the SGLT2 receptor is incorrect. SGLT2 inhibitors (i.e. dapagliflozin) work by preventing the kidneys from reabsorbing glucose back into the blood.

Reduced insulin resistance is incorrect. Thiazolidinediones (i.e. pioglitazone) are insulin sensitisers that enhance insulin action and increase insulin sensitivity in critical tissues.

👍 | 👎 | 💬 Discuss (2) | Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points
- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

PassMedicine

Question 328 of 414 ✗

A 56-year-old Muslim man with a history of type 2 diabetes asks for advice. He is due to start fasting for Ramadan soon and is unsure what he should do with regards to his diabetes medications. He currently takes metformin 500mg tds. What is the most appropriate advice?

	Switch to subcutaneous biphasic insulin for the duration of Ramadan	4%
🟩	500 mg at the predawn meal + 1000 mg at the sunset meal	58%
	No change to the metformin dose	21%
🟥	1000 mg at the predawn meal + 500 mg at the sunset meal	16%
	Stop metformin for the duration of Ramadan	2%

During Ramadan, one-third of the normal metformin dose should be taken before sunrise and two-thirds should be taken after sunset

Important for me Less important

Please see the Diabetes Care link for more details.

Discuss (5) Improve

Next question

Diabetes mellitus: Ramadan

We know that type 2 diabetes mellitus is more common in people of Asian ethnicity and a significant proportion of those patients in the UK will be Muslim. The BMJ published an excellent and comprehensive review of this issue in 2010[1].

It is important that we can give appropriate advice to Muslim patients to allow them safely observe their fast. This is particularly important from 2014 as Ramadan is due to fall in the long days of the summer months for several years henceforth.

Clearly it is a personal decision whether a patient decides to fast. It may however be worthwhile exploring the fact that people with chronic conditions are exempt from fasting or may be able to delay fasting to the shorter days of the winter months. It is however known that many Muslim patients with diabetes do not class themselves as having a chronic/serious condition which should exempt them from fasting. Around 79% of Muslim patients with type 2 diabetes mellitus fast Ramadan[2].There is an excellent patient information leaflet from Diabetes UK and the Muslim Council of Britain which explores these options in more detail.

If a patient with type 2 diabetes mellitus does decide to fast:
- they should try and and eat a meal containing long-acting carbohydrates prior to sunrise (Suhoor)
- patients should be given a blood glucose monitor to allow them to check their glucose levels, particularly if they feel unwell
- for patients taking metformin the expert consensus is that the dose should be split one-third before sunrise (Suhoor) and two-thirds after sunset (Iftar)
- expert consensus also recommends switching once-daily sulfonylureas to after sunset. For patients taking twice-daily preparations such as gliclazide it is recommended that a larger proportion of the dose is taken after after sunset
- no adjustment is needed for patients taking pioglitazone

1. Management of people with diabetes wanting to fast during Ramadan BMJ 2010;340:c3053
2. Salti I et al. Results of the Epidemiology of Diabetes and Ramadan (EPIDIAR) study. Diabetes Care 2004;27:2306-11.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Diabetes UK and Muslim Council 👍 4 👎 0

Patient information leaflet on the management of diabetes during Ramadan

Diabetes Care 👍 4 👎 1

Recommendations for Management of Diabetes During Ramadan

Report broken link

Score: **23.2%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
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14	✓
15	✗
16	✗
17	✓
18	✗
19	✗
20	✓
21	✓
22	✗

PassMedicine

Question 329 of 414 ✗

Which one of the following is least associated with gynaecomastia?

	Klinefelter's syndrome	11%
	Seminoma	26%
	Liver disease	4%
🟥	Puberty	14%
🟩	Hypothyroidism	46%

Gynaecomastia is seen in up to a third of men with thyrotoxicosis, but is not a feature of hypothyroidism

Discuss (3) Improve

Next question

Gynaecomastia

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis

- drugs: see below

Drug causes of gynaecomastia

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **23.1%**

PassMedicine

Question 330 of 414 ✗

A 58-year-old man attends the outpatient clinic for a diabetic review. He is a type 2 diabetic who was only diagnosed 8 months ago and started on metformin. He has had diabetic education from a nurse specialist and had tried dietary changes with limited benefit.

He has now developed two ulcers on his right foot and has been seeing his primary care practice nurse for regular dressing changes. A recent eye check showed progression from his previous background diabetic retinopathy.

His current body mass index is 35.5kg/m^2.

Blood tests 8 moths ago showed:

HbA1c	75 mmol/mol	(<48)

Repeat blood tests today show:

HbA1c today	74 mmol/mol	(<48)
Creatinine	110 µmol/L	(55 - 120)

What would be the most suitable second-line diabetic drug for this patient out of the options below?

🟥	Canagliflozin	19%
	Gliclazide	17%
	Insulin glargine (Lantus)	18%
	Pioglitazone	5%
🟩	Sitagliptin	41%

Gliptins (DPP-4 inhibitors) reduce the peripheral breakdown of incretins such as GLP-1

Important for me Less important

This was to test knowledge on how various second-line medications for diabetes work and which one would be most suitable for this patient. He is severely obese with worsening complications from his diabetes (retinopathy and now ulcer formation).

Second-line treatments for type 2 diabetes range from:
- Sulphonylureas e.g. gliclazide. Side effects include weight gain and hypoglycaemia.
- Gliptin's e.g. sitagliptin. Side effects include headaches, but are generally well tolerated.
- Thiazolidinedione e.g. pioglitazone. Side effects include fluid retention and weight gain.
- Sodium/glucose cotransporter 2 (SGLT-2) inhibitors e.g. canagliflozin. Side effects include urinary tract infections and increased risk of foot amputations (mainly with canagliflozin, but no evidence of a link with empagliflozin and dapagliflozin).

The correct choice here is sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor that works by inhibiting the breakdown of incretins in the gastrointestinal tract and therefore incretins can then stimulate insulin secretion. It is a good drug of choice for him given his severe obesity as it is associated with weight loss.

Now to look at the other options.

SGLT-2 inhibitors have very good evidence for improving cardiovascular and renal outcomes, but canagliflozin should be used with caution here as some evidence suggests an increased risk of foot amputations. Having two ulcers on this right foot should indicate either an alternative SGLT-2 inhibitor or, an alternative medication with a better side effect profile should be used. A better option would be empagliflozin if an SGLT-2 inhibitor were to be used here.

From the side effect profile, using sulphonylureas (e.g. gliclazide) would not be good for the patient due to him being severely obese. It is associated with weight gain, making other options better for him.

Insulin can cause weight gain and is reserved for when other treatments have provided inadequate control, so is not the correct option in this case.

Thiazolidinediones (e.g. pioglitazone) again can also result in weight gain and therefore would not be good for the patient due to his body mass index.

👍 👎 Discuss (12) Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*

> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

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NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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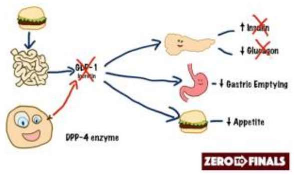

↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
GLP-1
DPP-4 enzyme
ZERO TO FINALS

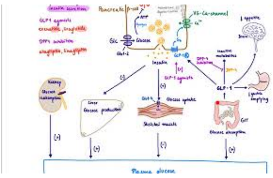
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2

The role of "GLP" system in Rx of diabetes
Sitagliptin
(-)
inactive GLP-1
DPP-4
incretin
"GLP"
↑ insulin release
↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 26 👎 5

Pharmacology of drugs used to treat type 2 diabetes

PassMedicine

Question 331 of 414 ✗

Which one of the following drugs used in the management of type 2 diabetes mellitus has the Medicines and Healthcare products Regulatory Agency warned is associated with an increased risk of severe pancreatitis and renal impairment?

	Rosiglitazone	28%
🟥	Metformin	6%
	Acarbose	12%
🟩	Exenatide	37%
	Sitagliptin	16%

The correct answer is **Exenatide**. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has issued a warning regarding the use of Exenatide, a glucagon-like peptide-1 (GLP-1) agonist, due to an increased risk of severe pancreatitis and renal impairment. Exenatide works by increasing insulin secretion, decreasing glucagon secretion, and slowing gastric emptying. However, studies have shown a correlation between its use and the development of severe pancreatitis and kidney damage.

Rosiglitazone is incorrect because it's not linked with an increased risk of severe pancreatitis or renal impairment according to MHRA. It's a thiazolidinedione which acts primarily by reducing insulin resistance. However, it has been associated with an increased risk of heart failure and bone fractures.

Metformin, while it can cause lactic acidosis especially in patients with renal impairment, is not associated with an increased risk of severe pancreatitis. Metformin is a biguanide that reduces hepatic glucose production and improves insulin sensitivity.

Acarbose also doesn't carry this warning from the MHRA. Acarbose is an alpha-glucosidase inhibitor which delays carbohydrate absorption from the gut but it may cause gastrointestinal side effects such as flatulence and diarrhoea.

Finally, **Sitagliptin**, a Dipeptidyl Peptidase-4 (DPP-4) inhibitor that prolongs the action of incretin hormones, isn't associated with an increased risk of severe pancreatitis or renal impairment according to MHRA guidelines. However, there are reports suggesting a possible link between

DPP-4 inhibitors and pancreatitis but these are currently inconclusive.

👍 👎 Discuss (7) Improve

Next question

Diabetes mellitus: GLP-1 drugs

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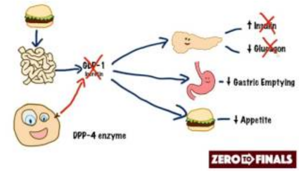
GLP-1
Incretin
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube

👍 45 👎 2

The role of "GLP" system in ℞ of diabetes
Slaughters the Peptidase
Sitagliptin
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Glucagon-like Peptide (GLP-1) and the treatment of diabetes

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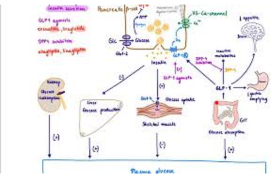

Type 2 diabetes agents and their mechanism of action

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← Question 332 of 414 ✗ →

A 60-year-old man is admitted to the endocrine ward following a one-month history of polyuria and polydipsia, he appears severely dehydrated. A water deprivation test is performed which shows the following result.

Urine osmolality post-fluid deprivation	50mOsm/kg	(50-1200)
Urine osmolality post-desmopressin	700mOsm/kg	(50-1200)

What is the diagnosis?

🟩	Cranial diabetes insipidus	77%
	Inconclusive result	2%
🟥	Nephrogenic diabetes insipidus	11%
	Primary polydipsia	6%
	Syndrome of inappropriate ADH secretion (SIADH)	4%

Water deprivation test: cranial DI

- urine osmolality after fluid deprivation: low
- urine osmolality after desmopressin: high

Important for me Less important

Cranial diabetes insipidus (DI) is the correct answer. ADH is secreted by the hypothalamus and acts on renal tubules to increase fluid reabsorption in response to fluid deprivation. In cranial diabetes insipidus, there is a failure of hypothalamic production of ADH. Accordingly, after fluid deprivation, urine is dilute due to a failure to reabsorb water from the urine in the absence of ADH production. However, following desmopressin administration, the urine will become concentrated as the renal tubules are still responsive to ADH, hence reabsorption occurs.

An inconclusive result is not correct - as explained above, the result is diagnostic for cranial diabetes insipidus.

Nephrogenic diabetes insipidus is incorrect, although clinically it would present in the same way.

In nephrogenic DI, although there is ADH production by the hypothalamus, there is a failure of the kidneys to respond to the hormone. Accordingly, following fluid deprivation, there is a failure to concentrate urine due to the absence of a renal tubular response to ADH. Following administration of desmopressin, the urine remains dilute as again, the kidneys do not respond to ADH.

Primary polydipsia is incorrect, although clinically it would present in the same way. In primary polydipsia excessive fluid intake occurs in the absence of a physiological stimulus to drink; there is adequate hypothalamic ADH production and an adequate renal tubular response to ADH. Therefore, following fluid deprivation the body is already able to effectively concentrate urine, and after desmopressin urine remains concentrated due to the presence of a renal tubular response to ADH.

SIADH is incorrect. SIADH is over-production of ADH in the absence of physiological stimuli. Clinically this would not cause polydipsia and polyuria, and patients would be euvolaemic or hypervolaemic, often with hyponatraemia. A fluid deprivation test cannot diagnose SIADH; urine osmolality is likely to be high due to excessive reabsorption of water due to excessive ADH production. More important in the diagnosis of SIADH is a paired urine and serum osmolality and sodium.

Discuss (1) Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder
- hourly urine and plasma osmolalities

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

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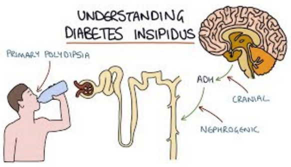
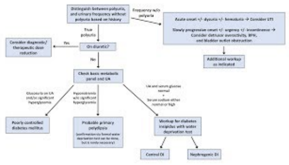

UNDERSTANDING
DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5



An Approach to Polyuria

Strong Medicine - YouTube 👍 29 👎 4

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Question 333 of 414 ✗

A 38-year-old woman presents to the emergency department with pain radiating from her right flank to her groin. She has a past medical history of Sjogren's syndrome. She takes hydroxychloroquine.

On examination, there is no evidence of peritonism.

Urinalysis:

Blood	++
Leucocytes	negative
Protein	negative
Glucose	negative

What is the probable underlying cause of her presentation?

	Hydroxychloroquine treatment	8%
🟩	Type 1 renal tubular acidosis	75%
	Type 2 renal tubular acidosis	11%
🟥	Type 3 renal tubular acidosis	2%
	Type 4 renal tubular acidosis	3%

Type 1 renal tubular acidosis (distal) complication - renal stones

Important for me Less important

Type 1 renal tubular acidosis is the correct answer. The patient's presentation is consistent with renal colic (haematuria, flank pain radiating to groin). Sjogren's syndrome is a cause of type 1 renal tubular acidosis and renal stones are a complication of this disorder.

Hydroxychloroquine treatment is incorrect. This medication is not associated with the development of renal stones. Common adverse effects of this medication include skin hyperpigmentation and dizziness. It is used commonly in the treatment of connective tissue diseases including Sjogren's syndrome.

Type 2 renal tubular acidosis is incorrect. This is proximal RTA caused by decreased HCO3- reabsorption in the proximal tubule. Complications include hypokalemia and osteomalacia. Causes include Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, and carbonic anhydrase inhibitors (acetazolamide, topiramate).

Type 3 renal tubular acidosis is incorrect. This rare disorder is caused by carbonic anhydrase II deficiency. Complications include hypokalemia but not renal stones.

Type 4 renal tubular acidosis is incorrect. This is caused by a reduction in aldosterone resulting in proximal tubular ammonium excretion causing hyperkalemia. Common causes include hypoaldosteronism and diabetes.

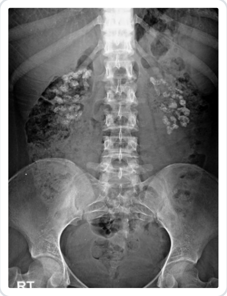
👍 👎 Discuss (3) Improve

Next question

Renal tubular acidosis ★

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)
- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Type 2 RTA (proximal)
- decreased HCO3- reabsorption in proximal tubule

- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 3 RTA (mixed)

- extremely rare
- caused by carbonic anhydrase II deficiency
- results in hypokalaemia

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

Next question

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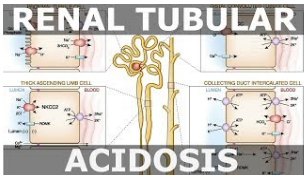

Renal tubular acidosis

DirtyUSMLE - YouTube 👍 177 👎 4

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Question 334 of 414

A 73-year-old woman presents to her general practitioner with complaints of urinary incontinence. She notices that when she coughs or laughs she leaks small amounts of urine and finds this very distressing. She has tried pelvic floor exercises and they haven't made a significant difference to her symptoms. She has no significant past medical history and is on no medications. She is a non-smoker and non-drinker. She has four children, all of whom were normal vaginal deliveries.

Examination reveals a raised body mass index (kg/m^2) but is otherwise unremarkable.

Her GP discusses options for the management of her problem with her and she is reluctant to consider surgery.

Given the likely diagnosis, what is the most appropriate next step in management?

	Bladder retraining	7%
🟩	Duloxetine	71%
	Mirabegron	12%
🟥	Oxybutynin	9%
	Tolterodine	2%

Duloxetine may be used in patients with stress incontinence who don't respond to pelvic floor muscle exercises and decline surgical intervention

Important for me Less important

Duloxetine is correct. This patient has stress incontinence as evidenced by the clinical history of incontinence precipitated by laughing and straining. She has risk factors for this type of incontinence including advanced age, childbirth and obesity. In patients who don't respond to pelvic floor muscle exercises and decline surgical intervention, duloxetine is a pharmacological option for treatment.

Bladder retraining is incorrect. This is a method of treating urge rather than stress incontinence.

Mirabegron is incorrect. This is a medication used in the management of urge incontinence and is particularly indicated where there is concern regarding anti-cholinergic side effects of more commonly used medications.

Oxybutynin is incorrect. This is a first line antimuscarinic treatment option for urge incontinence. It should be avoid however, in frail older women.

Tolterodine is incorrect. This is also used in urge, rather than stress, incontinence.

👍 👎 Discuss (3) Improve

Next question

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation
- bladder diaries should be completed for a minimum of 3 days

- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
    - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
    - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
    - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
    - a combined noradrenaline and serotonin reuptake inhibitor
    - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

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Question 335 of 414 ✗

Which one of the following increases the risk of developing peripheral oedema in a patient taking pioglitazone?

	Concomitant use with gliclazide	30%
	Serum sodium < 140 mmol/l	26%
🟩	Concomitant use with insulin	29%
🟥	Concomitant use with metformin	9%
	Serum potassium < 4.0 mmol/l	5%

The correct answer is **Concomitant use with insulin**. Pioglitazone, a thiazolidinedione class of drug used in the management of type 2 diabetes mellitus, is known to cause fluid retention and peripheral oedema. This side effect may be exacerbated when pioglitazone is used concurrently with insulin, as insulin also has the potential to cause fluid retention. Therefore, concomitant use of these two drugs increases the risk of developing peripheral oedema.

Concomitant use with gliclazide does not increase the risk of peripheral oedema. Gliclazide, a second-generation sulfonylurea antidiabetic medication, primarily works by increasing insulin secretion from the pancreas but it does not have a significant effect on fluid balance or contribute to peripheral oedema.

Serum sodium < 140 mmol/l, or hyponatraemia, does not directly increase the risk of peripheral oedema in patients taking pioglitazone. Although severe hyponatraemia can lead to cellular swelling due to osmotic shifts, this typically manifests as neurological symptoms rather than peripheral oedema.

Concomitant use with metformin, like gliclazide, also does not increase the risk of peripheral oedema. Metformin is an oral antidiabetic drug that primarily works by decreasing hepatic glucose production and improving insulin sensitivity. It does not have any notable effects on fluid balance.

Finally, **Serum potassium < 4.0 mmol/l**, or hypokalaemia, while it can cause muscle weakness and cardiac arrhythmias among other symptoms, it doesn't directly increase the risk of developing peripheral oedema in patients taking pioglitazone.

Discuss (7) Improve

Next question

Thiazolidinediones

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. It's natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

Next question

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← Question 336 of 414 ✗ →

Which one of the following skin disorders is least associated with hypothyroidism?

	Xanthomata	18%
	Pruritus	15%
🟩	Pretibial myxoedema	48%
🟥	Eczema	13%
	Dry, coarse hair	6%

For the purposes of postgraduate exams pretibial myxoedema is associated with thyrotoxicosis. There are however case reports of it been found in hypothyroid patients, especially the diffuse non-pitting variety

Discuss (4) Improve

Next question

Skin disorders associated with thyroid disease ★

Skin manifestations of hypothyroidism

- dry (anhydrosis), cold, yellowish skin
- non-pitting oedema (e.g. hands, face)
- dry, coarse scalp hair, loss of lateral aspect of eyebrows
- eczema
- xanthomata

Skin manifestations of hyperthyroidism

- pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli
- thyroid acropachy: clubbing
- scalp hair thinning
- increased sweating

Pruritus can occur in both hyper- and hypothyroidism

Next question

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Links

DermIS.net 👍 1 👎 2

Pictures of pretibial myxoedema

Report broken link

Score: **22.6%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

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Question 337 of 414 ✗

Each one of the following is associated with Pendred's syndrome, except:

	Goitre	9%
🟩	Short 4th and 5th metacarpals	39%
	Autosomal recessive inheritance	13%
🟥	Sensorineural deafness	9%
	Euthyroid status	30%

The correct answer is **Short 4th and 5th metacarpals**. Pendred's syndrome, a form of syndromic deafness, is not associated with short 4th and 5th metacarpals. This feature is typically seen in conditions such as Albright's hereditary osteodystrophy (pseudohypoparathyroidism), which presents with a constellation of symptoms including short stature, round face, subcutaneous calcifications, and resistance to parathyroid hormone.

Goitre is indeed associated with Pendred syndrome. This condition results from mutations in the SLC26A4 gene that leads to impaired iodide organification during thyroid hormone synthesis, causing enlargement of the thyroid gland or goitre. However, the goitre usually develops in later childhood or early adulthood and may not be present in all individuals with Pendred's syndrome.

Autosomal recessive inheritance is also correct for Pendred's syndrome. It follows this pattern of inheritance where two copies of an abnormal gene must be present for the disease to develop. Both parents must be carriers but typically do not show signs and symptoms of the condition.

Sensorineural deafness is a key feature of Pendred's syndrome. The mutation in SLC26A4 gene affects the function of inner ear cells responsible for maintaining fluid balance, leading to swelling and damage that result in sensorineural hearing loss. The severity varies among affected individuals but it often starts before language development.

Finally, **Euthyroid status** refers to having normal thyroid function despite the presence of goitre - another characteristic feature common in patients with Pendred's syndrome. Although they have goitres due to impaired iodide organification caused by mutations in SLC26A4 gene, these individuals are typically euthyroid meaning their thyroid hormone levels (T3 & T4) remain normal because they can compensate for this defect by increasing thyroglobulin production.

Discuss (2) Improve

Next question

Pendred's syndrome ★

Pendred is an autosomal recessive genetic disorder that is characterised by bilateral sensorineural deafness, with mild hypothyroidism and a goitre. The patients tend to present with progressive hearing loss and delay in academic progression. Often head trauma tends to make the sensorineural deafness worse, leading to patients having to avoid contact sports.

In Pendred syndrome there is a defect in the organification of iodine, leading to dyshormonogenesis. However thyroid symptoms in pendred syndrome are often mild and patients are often clinically euthyroid, presenting only with a goitre. Thyroid function tests are also often normal, requiring the perchlorate discharge test to aid diagnosis.

The syndrome can be diagnosed via genetic testing (Pendred syndrome (PDS) gene, chromosome 7), audiometry and MRI imaging to look for characteristic one and a half turns in the cochlea, compared to the normal two and a half turns.

Treatment is with thyroid hormone replacement and cochlear implants.

Next question

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Question 338 of 414 ✓

Mr Bevan is a 52-year-old patient with type 2 diabetes. He was unable to tolerate metformin due to nausea. He has been doing some of his own research into other options and suggests an SGLT-2 inhibitor, empagliflozin, because he has read it might help him lose weight and improve his blood pressure, as well as improve his blood sugar.

What is the mechanism of action of this drug?

Increase insulin release from pancreas	4%
Decrease glucose absorption in the gut	6%
Decrease glucagon release from pancreas	2%
Increase urinary glucose excretion	86%
Slows gastric emptying	1%

SGLT-2 inhibitors work by increasing urinary excretion of glucose
(Important as it is the cause of main side effects - increased urine output, weight loss, UTI)

Important for me Less important

Increase insulin release from pancreas - this is the mechanism of action of sulphonylureas e.g. gliclazide.

Decrease glucose absorption in the gut - this is the mechanism of action of acarbose, which is not routinely prescribed in the UK.

Decrease glucagon release from pancreas - DPP4-inhibitors reduce the breakdown of incretins, which thereby decreases glucagon secretion.

SGLT-2 inhibitors such as empagliflozin work by reducing glucose reabsorption in the proximal convoluted tubule, therefore increasing the amount of glucose excreted in the urine. An additional 70g of glucose a day (approximately) is excreted; as well as improving blood sugar this is also likely to lead to weight loss, in contrast to some other diabetic medications such as sulphonylureas and insulin which cause weight gain. The slight diuresis caused by increased glucose excretion may also improve blood pressure. Unfortunately, increased glucose in the urine can also cause adverse events such as urinary tract or genital infections.

SGLT-2 inhibitors do not slow gastric emptying.

👍 👎 Discuss (2) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

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← Question 339 of 414 ✗ ⚐ →

John is a 16-year-old male who reviewed in the clinic due to concerns around his development. His growth has not progressed as expected and he remains shorter than most of the boys in school. He also notes that he has not grown any facial hair which is affecting his confidence.

Examination reveals that he is 155cm tall. He has sparse pubic hair with little axillary hair. Testicular volume was measured at 3mls. Penile length measured at 3 inches. A cleft palate is noted on examination of the mouth. When cranial nerve I was examined, he was unable to detect the smell of the odours sampled.

Blood tests show a low level of testosterone, follicular stimulating hormone (FSH) and luteinizing hormone (LH). Liver function tests were normal. Blood glucose reading was 5.6mmol/L. Iron studies were unremarkable.

What is the likely cause for his symptoms?

	Haemochromatosis	1%
🟥	Histiocytosis X	2%
🟩	Kallmann syndrome	82%
	Klinefelter syndrome	12%
	Turner syndrome	4%

Kallman's syndrome - LH & FSH low-normal and testosterone is low

Important for me Less important

This patient presents with signs of pubertal delay and poor secondary sexual development. This combined with the anosmia, cleft palate and blood tests point towards Kallmann syndrome. Low FSH, LH and testosterone signify hypogonadotropic hypogonadism. Kallmann syndrome is a recognized cause of congenital hypogonadotropic hypogonadism and is X-linked inherited. This caused by the failure of migration of gonadotrophin-releasing hormone-producing neurons within the developing brain.

Klinefelter syndrome is another congenital cause for poor pubertal development. This can be associated with small testes and delayed pubertal development. The cause for the poor pubertal development is due to hypergonadotropic hypogonadism and blood tests will show raised FSH and LH but low testosterone levels. Anosmia is also not a common feature.

Haemochromatosis is a possible cause for hypogonadotropic hypogonadism due to deposition of iron into the hypothalamus. This is not likely in this case due to the normal iron study and anosmia is also not a common feature.

Turner syndrome is a congenital cause of hypergonadotropic hypogonadism rather than hypogonadotropic hypogonadism. Also, as the patient genotype is typically XO, patients will tend to have genitalia consistent with the female gender rather than male genitalia.

Histiocytosis X is a rare cause of hypogonadotropic hypogonadism. It is caused by the proliferation of Langerhans cells and causes symptoms due to infiltration into other organs. Infiltration into the pituitary glands is the cause of hypogonadism. It is less likely in this case due to the lack of other body system involvement like skin or lung involvement.

👍 | 👎 | 💬 Discuss (2) | Improve

Next question

Kallmann's syndrome ★

Kallmann's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallmann's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty.

Features
- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above-average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Management

- testosterone supplementation
- gonadotrophin supplementation may result in sperm production if fertility is desired later in life

Next question

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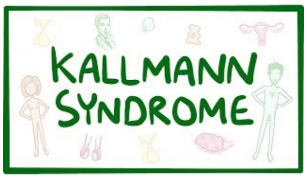
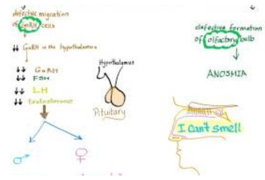
Media


KALLMANN
SYNDROME

Kallman's syndrome

Osmosis - YouTube 👍 42 👎 1


defective migration
Pituitary
defective formation of olfactory bulb
ANOSMIA
I can't smell

Kallmann Syndrome mnemonic

Medicosis Perfectionalis - YouTube 👍 7 👎 6

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Question 340 of 414 ✗

A 75-year-old woman presents with weight gain, lethargy and constipation. She says that she has not changed her diet but has started 'piling on the pounds'. She also feels 'bunged up' and is only opening her bowels twice a week, and she used to go daily. She has doubled her dose of senna but this hasn't made much difference. She has a past medical history of hypothyroidism and has recently been diagnosed with angina and iron deficiency anaemia. She takes nifedipine, atorvastatin, aspirin, senna, levothyroxine and ferrous sulphate.

Which of her medications is most likely to be the cause of this presentation?

	Nifedipine	16%
	Atorvastatin	3%
🟥	Aspirin	1%
	Senna	3%
🟩	Ferrous sulphate	77%

Iron / calcium carbonate tablets can reduce the absorption of levothyroxine - should be given 4 hours apart

Important for me Less important

Ferrous sulphate is correct. This woman is presenting with symptoms of hypothyroidism - weight gain, lethargy and constipation. This is despite treatment with levothyroxine, indicating that the hypothyroidism is effectively undertreated.

Tablets containing iron can reduce the absorption of levothyroxine, and as these have recently been started, this is the likely cause of the symptoms. Tablets containing iron and levothyroxine should be taken at least 2 and preferably over 4 hours apart to prevent this effect.

There is no interaction between levothyroxine and any of the other medications.

Discuss (4) Improve

Next question

Hypothyroidism: levothyroxine therapy

Key points

- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value
- there is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy

- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions

- iron, calcium carbonate
    - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

Next question

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Links

Clinical Knowledge Summaries 👍 7 👎 6

Management of hypothyroidism

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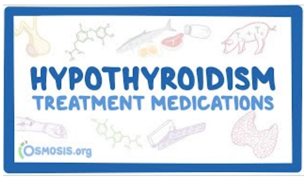
Media


HYPOTHYROIDISM
TREATMENT MEDICATIONS
OSMOSIS.org

Hypothyroidism treatment medications

Osmosis - YouTube 👍 4 👎 1

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Score: **22.6%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

PassMedicine

Question 341 of 414 ✗

A 45-year-old woman is seen in the endocrinology clinic.

She complains of an 8-month history of tiredness, nausea, and vomiting. She also gets dizzy when she stands up.

On examination, she has marked pigmentation of the palmar creases in her hands. Her lying and standing blood pressure measurements show a drop of 31mmHg.

Her relevant blood tests are shown below:

Na^+	129 mmol/L	(135 - 145)
K^+	5.1 mmol/L	(3.5 - 5.0)
Bicarbonate	20 mmol/L	(22 - 29)
Urea	4.4 mmol/L	(2.0 - 7.0)
Creatinine	67 µmol/L	(55 - 120)

Given the likely cause, what test is most likely to be diagnostic?

9 AM cortisol levels	9%
High-dose dexamethasone suppression test	9%
Low-dose dexamethasone suppression test	7%
Short synacthen test	73%
Water deprivation test	2%

The short synacthen test is the best test to diagnose Addison's disease

Important for me Less important

Short synacthen test is correct. This patient is exhibiting the signs and symptoms of adrenal insufficiency. Diagnosis of adrenal insufficiency can be made using the short synacthen test (or ACTH simulation test). A dose of synthetic ACTH is given, and normally functioning adrenal glands respond by producing cortisol, which is then measured. In cases of Addison's disease (primary adrenal insufficiency), the adrenal glands cannot respond. This will be reflected in the absence of a cortisol increase in response to the synthetic ACTH.

9 AM cortisol levels is incorrect. This is a good initial screening test for steroid deficiency; a result of < 140 nanomols/L suggests deficiency. 9 AM cortisol levels are useful for *excluding* primary adrenal insufficiency, but a definitive diagnosis of primary adrenal insufficiency requires a short synacthen test. This answer is therefore incorrect.

High-dose dexamethasone suppression test is incorrect. This would be used in cases of suspected hypercortisolism when the patient has not suppressed their cortisol levels in response to the low-dose dexamethasone suppression test. If suppression of the cortisol levels is then achieved with the high dose of dexamethasone, this suggests Cushing's disease, rather than ectopic ACTH production or a steroid-secreting adrenal tumour.

Low-dose dexamethasone suppression test is incorrect. This is used to identify cases of Cushing's syndrome. In an individual without Cushing's syndrome, a low dose of dexamethasone will suppress cortisol. In Cushing's syndrome, the cortisol is not suppressed. These individuals may then go on to the high-dose test to differentiate Cushing's disease from ectopic ACTH production or a steroid-secreting adrenal tumour.

Water deprivation test is incorrect. This is used in the diagnosis of diabetes insipidus. In the water deprivation test, the initial serum and urine osmolalities are checked. Following water deprivation, urine osmolality should increase. The test can then be stopped without progressing to desmopressin as diabetes insipidus has been excluded. If the urine osmolality fails to increase, this suggests diabetes insipidus. Desmopressin is then administered to determine whether the diabetes insipidus is cranial or nephrogenic in origin. The test is not used to diagnose adrenal insufficiency.

👍 👎 Discuss Improve

Next question

Addison's disease: investigations ★

In a patient with suspected Addison's disease the definite investigation is an ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If an ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:

- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

Next question

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Links

Royal College of Physicians 👍 6 👎 4

2017 Adrenal insufficiency â€“ recognition and management

Report broken link

Media

Primary adrenal insufficiency (Addison's disease)

Osmosis - YouTube

PassMedicine

Question 342 of 414 ✗

A 44-year-old woman presents to her GP as she is feeling 'hot all the time' and is consequently worried she is going through an early menopause. Her husband has also noticed a 'fullness' of her neck which has become apparent over the past few weeks. On examination her pulse is 90/minute and she has a small, non-tender goitre. Blood tests are arranged:

TSH	< 0.05 mu/l
Free T4	24 pmol/l
Anti-thyroid peroxidase antibodies	102 IU/mL (< 35 IU/mL)
ESR	23 mm/hr

What is the most likely diagnosis?

Hashimoto's thyroiditis	34%
Toxic multinodular goitre	5%
🟥 Thyroid cancer	1%
De Quervain's thyroiditis	7%
🟩 Graves' disease	54%

The thyrotoxic symptoms and blood tests, goitre and anti-thyroid peroxidase antibodies suggest a diagnosis of Graves' disease.

Whilst anti-thyroid peroxidase antibodies are seen in 90% of Hashimoto's disease they are also seen in 75% of patients with Graves' disease. Hashimoto's thyroiditis is also generally associated with hypothyroidism, which is not in keeping with this presentation.

The ESR result is within normal range.

Discuss (9) | Improve

Next question

Graves' disease: features ★

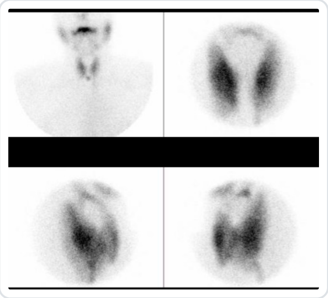
Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis
- eye signs (30% of patients)
    - exophthalmos
    - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
    - digital clubbing
    - soft tissue swelling of the hands and feet
    - periosteal new bone formation

Autoantibodies
- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

Thyroid scintigraphy
- diffuse, homogenous, increased uptake of radioactive iodine



Next question

Textbooks

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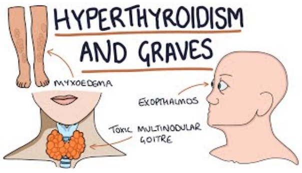
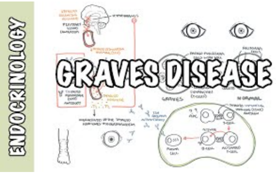
Media


HYPERTHYROIDISM AND GRAVES
MYXOEDEMA
EXOPTHALMOS
TOXIC MULTINODULAR GOITRE

Understanding Hyperthyroidism and Graves' Disease

Zero to Finals - YouTube 👍 25 👎 2


ENDOCRINOLOGY
GRAVES DISEASE

Graves' disease

Armando Hasudungan - YouTube 👍 14 👎 3

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Score: **22.5%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗

PassMedicine

Question 343 of 414 ×

A 52-year-old man with type 2 diabetes mellitus presents to the Endocrinology clinic for review. He is currently established on treatment with metformin and glibenclamide, both of which have been maximally up-titrated. In spite of this, his HbA1c reading has risen from 58 mmol/mol to 67 mmol/mol in the last six months. As such, his consultant suggests adding sitagliptin as a third antidiabetic medication.

What best describes the mechanism of action of this new medication?

Activate peroxisome proliferator-activated receptor gamma (PPAR-Î³) to increase insulin sensitivity	7%
Decrease blood glucose by inhibiting renal glucose re-uptake via sodium-glucose co-transporter 2(SGLT2)	9%
Inhibit the peripheral breakdown of incretins, enhancing their ability to stimulate insulin release	66%
Mimic incretins by binding to GLP-1 receptors and stimulating insulin release	15%
Trigger the closure of ATP-sensitive K+ channels, stimulating insulin exocytosis	3%

DPP-4 inhibitors increase levels of incretins such as GLP-1 and GIP

Important for me Less important

The correct answer is **inhibit the peripheral breakdown of incretins, enhancing their ability to stimulate insulin release**. Sitagliptin is an inhibitor of the enzyme dipeptidyl-peptidase 4 (DPP-4). As such, it prevents DPP-4 from catalysing the breakdown of naturally occurring incretins, potentiating their ability to stimulate insulin release.

Activate peroxisome proliferator-activated receptor gamma (PPAR-Î³) to increase insulin sensitivity is incorrect. This is the mechanism by which thiazolidinediones such as pioglitazone reduce blood glucose.

Decrease blood glucose by inhibiting renal glucose re-uptake via sodium-glucose co-transporter 2(SGLT2) is incorrect. This describes the mechanism of action of SGLT2 inhibitors such as dapagliflozin.

Mimic incretins by binding to GLP-1 receptors and stimulating insulin release is incorrect. This is how GLP-1 receptor agonists such as exenatide promote insulin release and lower blood glucose.

Trigger the closure of ATP-sensitive K+ channels, stimulating insulin exocytosis is incorrect as this is the mechanism of action of sulfonylureas such as glibenclamide, rather than DPP-4 inhibitors.

👍 👎 Discuss Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m² in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points
- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

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Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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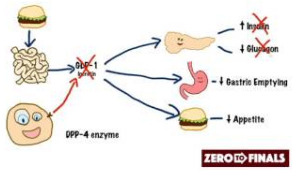
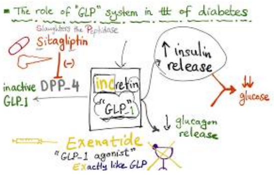
Media


GLP-1
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

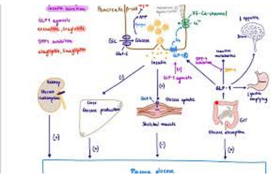
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2


The role of "GLP" system in tt of diabetes
Slaughters the Peptidase
Sitagliptin
(−)
inactive GLP-1
DPP-4
incretin
"GLP" 1
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
EXactly like GLP

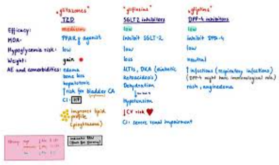
Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



[Type 2 diabetes agents and their mechanism of action]

Brandl's Basics - YouTube 👍 26 👎 5



[Pharmacology of drugs used to treat type 2 diabetes]

Brandl's Basics - YouTube 👍 23 👎 7

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Score: **22.4%**

1	✓
2	✓
3	✓
4	✗
5	✗
6	✗
7	✗
8	✗
9	✓
10	✗
11	✗
12	✓
13	✗
14	✓
15	✗
16	✗
17	✓

PassMedicine

Question 344 of 414 ✗

A 54-year-old man is brought to the Emergency Department after being found collapsed in the street. He is known to have a history of alcoholic liver disease. Blood tests reveal the following:

Calcium	1.62 mmol/l
Albumin	33 g/l

Which one of the following is the most appropriate management of the calcium result?

	10ml of 10% calcium chloride over 10 minutes	17%
	20% albumin infusion	3%
🟩	10ml of 10% calcium gluconate over 10 minutes	68%
🟥	No action	6%
	10ml of 10% calcium chloride over 4 hours	6%

Intravenous calcium gluconate is used for the acute management of hypocalcaemia

Important for me Less important

Even after correction for the low albumin level this patient has significant hypocalcaemia which should be corrected.

Discuss (4) Improve

Next question

Hypocalcaemia: causes and management

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- vitamin D deficiency (osteomalacia)
- chronic kidney disease
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion
- acute pancreatitis

Contamination of blood samples with EDTA may also give falsely low calcium levels.

Management

- severe hypocalcaemia (e.g. carpopedal spasm, tetany, seizures or prolonged QT interval) requires IV calcium replacement
    - the preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
    - intravenous calcium chloride is more likely to cause local irritation
    - ECG monitoring is recommended
- further management depends on the underlying cause

Next question

Textbooks

High-yield textbook

Extended textbook

Media

A 57-year-old woman attends the endocrine clinic.

Her medical history includes non-insulin-dependent diabetes, hypertension, a BMI of 36 kg/m^2 and ischaemic heart disease.

Her medications include metformin, empagliflozin, and gliclazide. She states she is compliant with all her medications.

Her most recent Hb A1c show:

Hb A1c	72 mmol/mol	Today	(> 48)
Hb A1c	70 mmol/mol	Three months ago	(> 48)

She is switched from gliclazide to another medication.

What medication should be started in place of gliclazide?

🟩	Liraglutide	61%
🟥	Long-acting insulin	5%
	Pioglitazone	5%
	Repaglinide	5%
	Sitagliptin	25%

> TD2M: if a triple combination of drugs has failed to reduce HbA1c then switching one of the drugs for a GLP-1 mimetic is recommended, particularly if the BMI > 35
>
> Important for me Less important

Liraglutide is a daily injectable GLP-1 mimetic that has been proven to reduce cardiovascular events in patients with type 2 diabetes. GLP-1 mimetics can aid in weight management especially when the BMI is > 35 kg/m^2. Side effects of GLP-1 mimetics include gastrointestinal upset, acute pancreatitis, and cholelithiasis. Gliclazide, a sulphonylurea, is proven to help glycaemic control but this drug class has not been associated with the reduction of cardiovascular events in patients with type 2 diabetes.

Long-acting insulin is a valid option for this woman due to the failed triple combination of medications. However, insulin is associated with weight gain and has not been shown to reduce cardiovascular events in patients with type 2 diabetes. A trial of a GLP-1 mimetic is the most appropriate option for this woman at present. If her Hb A1c were to continue to increase, starting insulin in combination with a GLP-1 mimetic would be appropriate.

Pioglitazone is a PPAR-*γ* receptor agonist that was used commonly but its use has decreased over recent years due to the emergence of newer diabetic medications. A side effect of pioglitazone is an increase in subcutaneous adipose tissue. Therefore, this medication is not appropriate for this woman. Pioglitazone is contraindicated in patients with heart failure due to the side effect of fluid retention.

Repaglinide is an insulin secretagogue where it stimulates insulin release by binding to the islet beta cell receptors. Side effects of repaglinide include hypoglycaemia and weight gain since it stimulates insulin release. This unfavourable side effect profile makes repaglinide an inappropriate option for this woman.

Sitagliptin is a DPP-4 inhibitor that breaks down incretins such as GLP-1 to increase the secretion of insulin. Sitagliptin does not affect weight. Thus, liraglutide might be a better option for this particular patient due to its potential for weight loss. Common side effects of sitagliptin include headache and gastrointestinal upset.

Discuss Improve

Next question

Diabetes mellitus: management of type 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

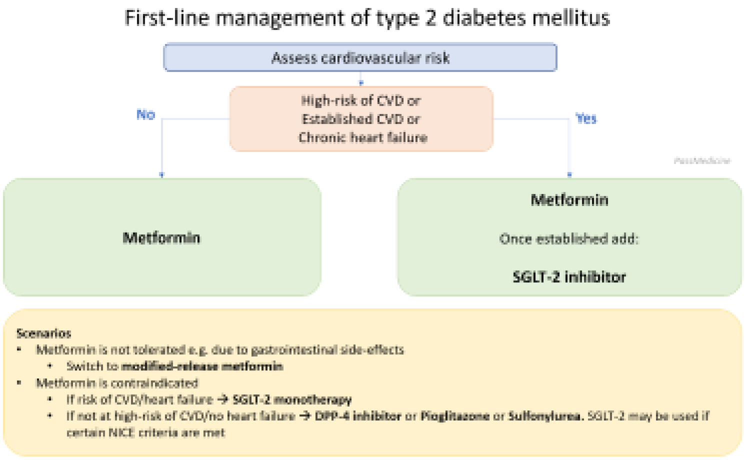
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios
- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

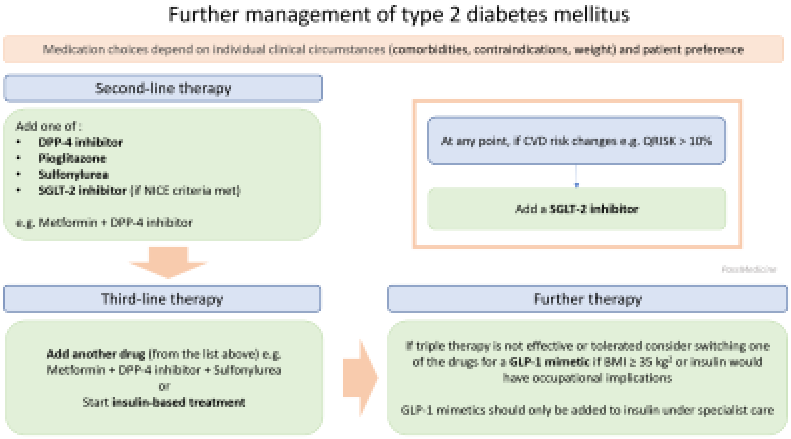
Metformin remains the first-line drug of choice in type 2 diabetes mellitus.
- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

SGLT-2 inhibitors
- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated
- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:

  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

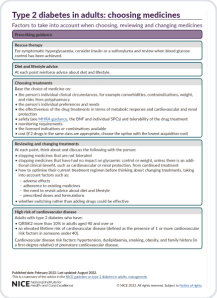
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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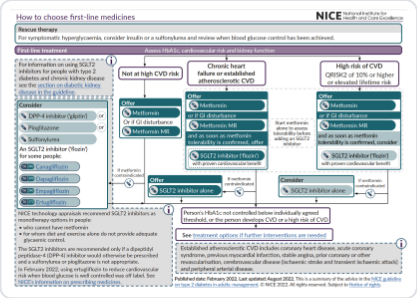

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment
Assess HbA1c, cardiovascular risk and kidney function
Not at high CVD risk
Chronic heart failure or established atherosclerotic CVD
High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
Or if GI disturbance
Metformin MR
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit
Start metformin alone to assess tolerability before adding an SGLT2 inhibitor
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit
If metformin contraindicated
Offer
SGLT2 inhibitor alone
If metformin contraindicated
Consider
SGLT2 inhibitor alone
If metformin contraindicated
Consider
DPP-4 inhibitor ('gliptin')
or
Pioglitazone
or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD
See treatment options if further interventions are needed

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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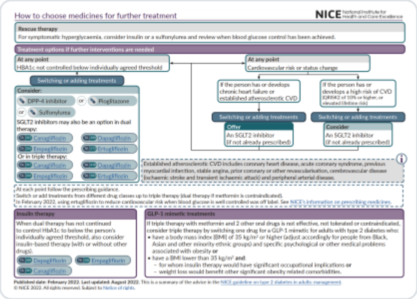

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point

HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider:

DPP-4 inhibitor or Pioglitazone or Sulfonylurea

SGLT2 inhibitors may also be an option in dual therapy:

Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

Or in triple therapy:

Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

At any point

Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD

Switching or adding treatments

Offer

An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)

Switching or adding treatments

Consider

An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.

Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

Dapagliflozin, Empagliflozin, Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m² or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m² **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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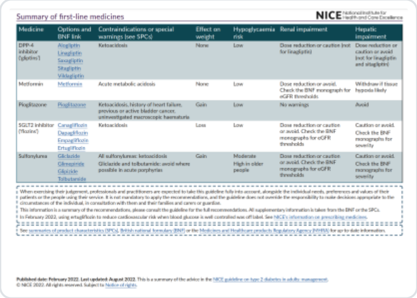

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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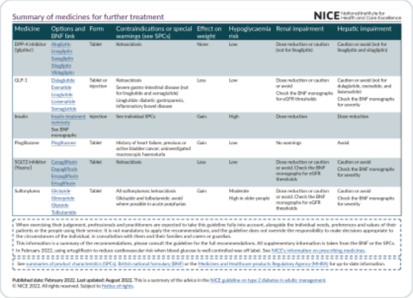

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

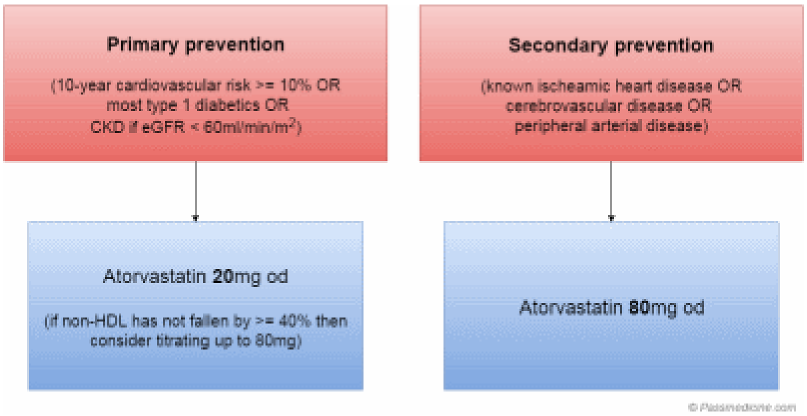
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischaemic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

PassMedicine

Question 346 of 414 ✓

Which of the following is most likely to cause hypokalaemia associated with alkalosis?

Acetazolamide	12%
Partially treated diabetic ketoacidosis	2%
Diarrhoea	19%
Cushing's syndrome	57%
Renal tubular acidosis	10%

Cushing's syndrome causes hypokalaemia with alkalosis

Important for me Less important

The correct answer is **Cushing's syndrome**. Hypokalaemia and metabolic alkalosis are common features of Cushing's syndrome. This is due to increased levels of cortisol, which can lead to the activation of mineralocorticoid receptors in the distal tubules, leading to increased reabsorption of sodium and excretion of hydrogen and potassium ions. This results in hypokalaemia and alkalosis.

Acetazolamide is a carbonic anhydrase inhibitor that is used as a diuretic. It works by inhibiting the reabsorption of bicarbonate in the proximal tubules, leading to bicarbonaturia and a resultant metabolic acidosis rather than alkalosis. It can cause hypokalaemia, but is not usually associated with alkalosis.

Partially treated diabetic ketoacidosis (DKA) typically presents with hyperkalaemia rather than hypokalaemia due to acidosis-induced shifts of potassium from intracellular to extracellular spaces. Additionally, DKA leads to metabolic acidosis, not alkalosis.

In cases of severe or prolonged **diarrhoea**, there may be significant potassium loss resulting in hypokalaemia. However, this is usually associated with non-anion gap metabolic acidosis (due to loss of bicarbonate) rather than alkalosis.

Finally, **renal tubular acidosis (RTA)** refers to a group of disorders that affect the renal tubules' ability to reabsorb filtered bicarbonate or excrete hydrogen ions. Type 1 RTA (distal) and type 2 RTA (proximal) both result in a normal anion gap metabolic acidosis rather than alkalosis although they may also present with hypokalaemia.

Discuss (5) Improve

Next question

Hypokalaemia

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalaemia with alkalosis
- vomiting
- thiazide and loop diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis
- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

Next question

B I A T↕

Textbooks

PassMedicine

← Question 347 of 414 ✗ ⚐ →

Which of the following statements is true regarding the pathophysiology of diabetes mellitus?

🟩	Concordance between identical twins is higher in type 2 diabetes mellitus than type 1	47%
	Patients with type 1 diabetes mellitus are rarely HLA-DR4 positive	12%
	Type 2 diabetes mellitus is associated with HLA-DR3	18%
🟥	Haemochromatosis is an example of primary diabetes	5%
	Type 1 diabetes mellitus is thought to be inherited in an autosomal dominant fashion	18%

Type 1 diabetes mellitus is caused by autoimmune destruction of the Beta-cells of the pancreas. Identical twins show a genetic concordance of 40%. It is associated with HLA-DR3 and DR4. It is inherited in a polygenic fashion

Type 2 diabetes mellitus is thought to be caused by a relative deficiency of insulin and the phenomenon of insulin resistance. Age, obesity and ethnicity are important aetiological factors. There is almost 100% concordance in identical twins and no HLA associations.

Haemochromatosis is an example of secondary diabetes

Discuss (2) | Improve

Next question

Diabetes: pathophysiology ★

Type 1 DM
- autoimmune disease
- antibodies against beta cells of pancreas
- HLA DR4 > HLA DR3
- various antibodies such as islet-associated antigen (IAA) antibody and glutamic acid decarboxylase (GAD) antibody are detected in patients who later go on to develop type 1 DM

PassMedicine

← Question 348 of 414 ✗ ⚐ →

A 46-year-old woman is referred to endocrine with a tender neck swelling. Blood results are as follows:

TSH	<0.1 mU/l
T4	188 nmol/l
Hb	14.2 g/dl
Plt	377 * 10^9/l
WBC	6.4 * 10^9/l
ESR	65 mm/hr

Technetium thyroid scan shows decreased uptake globally

What is the most likely diagnosis?

Sick thyroid syndrome	5%
Acute bacterial thyroiditis	5%
🟥 Hashimoto's thyroiditis	17%
🟩 Subacute thyroiditis	62%
Toxic multinodular goitre	12%

Subacute thyroiditis is suggested by the tender goitre, hyperthyroidism and raised ESR. The globally reduced uptake on technetium thyroid scan is also typical

👍 👎 Discuss (6) Improve

Next question

Subacute (De Quervain's) thyroiditis ★

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;

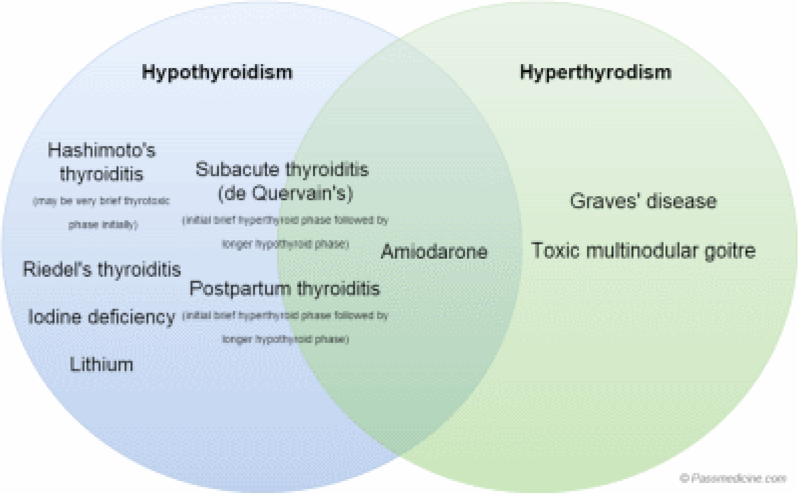
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

Investigations

- thyroid scintigraphy: globally reduced uptake of iodine-131

Management

- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Graves' disease
Toxic multinodular goitre
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

Next question

PassMedicine

Question 349 of 414 ✗

A 25-year-old Asian woman who is 26 weeks pregnant has an oral glucose tolerance test (OGTT). This was requested due to a combination of her ethnicity and a background of obesity. A recent ultrasound shows that the fetus is large for dates. The following results are obtained:

Time (hours)	**Blood glucose (mmol/l)**
0	9.2
2	14.2

What is the most appropriate management?

🟩	Start insulin	61%
	Give advice about a diabetic diet	2%
	Give advice about a diabetic diet + repeat OGTT in 4 weeks	7%
🟥	Start gliclazide	1%
	Start metformin	30%

Insulin should be started straight away given the blood glucose levels and evidence of macrosomia. Aspirin should also be considered as she is at increased risk of pre-eclampsia.

Discuss (3) Improve

Next question

Gestational diabetes

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:

- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes

- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes
- BMI of > 30 kg/m^2
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes
- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes
- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes
- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered

- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

High-yield textbook

Extended textbook

Links

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Question 350 of 414 ✓

A 68-year-old woman attends the clinic with a 1-month history of excessive thirst. She has a history of biventricular heart failure for which she takes ramipril, bisoprolol and furosemide.

Blood results are as follows:

Hb	105 g/L	Male: (135-180) Female: (115 - 160)
Platelets	152 * 10 ^{9}/L	(150 - 400)
WBC	9.6 * 10 ^{9}/L	(4.0 - 11.0)
Na^+	136 mmol/L	(135 - 145)
K^+	3.8 mmol/L	(3.5 - 5.0)
Urea	7.6 mmol/L	(2.0 - 7.0)
Creatinine	108 µmol/L	(55 - 120)
CRP	46 mg/L	(< 5)

Calcium	3.2 mmol/L	(2.1-2.6)
Phosphate	0.62 mmol/L	(0.8-1.4)
PTH	0.4 pmol/L	(1.6 - 6.9)

What is the most likely cause?

Furosemide	13%
Malignancy	45%
Osteopenia	4%
Primary hyperparathyroidism	22%
Primary hypoparathyroidism	16%

In hypercalcaemia secondary to malignancy, PTH is low, although PTHrP may be raised

Important for me Less important

Malignancy is correct. Hypercalcaemia with suppressed PTH is highly suspicious for malignancy (e.g. solid organ, or myeloma). Alternative diagnoses which can cause this pattern include thyrotoxicosis.

Furosemide is incorrect. Furosemide is a loop diuretic agent that can cause hypocalcemia due to increased calcium excretion which increases the risk of kidney stones.

Osteopenia is incorrect. This is a quantitative, not qualitative, disorder of bone mineralisation. Laboratory bone profile results are usually normal, and the diagnosis relies on a DEXA scan.

Primary hyperparathyroidism is incorrect. This condition is characterised by hypercalcaemia with a raised or inappropriately normal PTH. The PTH levels are generally elevated in primary hyperparathyroidism, although approximately 10% to 20% of individuals will have 'inappropriately normal' levels. The suppressed PTH in this case makes this a very unlikely diagnosis.

Primary hypoparathyroidism is incorrect. This condition results in hypocalcaemia, rather than hypercalcaemia.

👍 👎 Discuss Improve

Next question

Hypercalcaemia: causes ★

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
    - PTHrP from the tumour e.g. squamous cell lung cancer
    - bone metastases
    - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include

- sarcoidosis

    - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:
    - thiazides
    - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
    - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€“ presentation and management

Report broken link

Media

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Question 351 of 414 ✗

A 54-year-old man is reviewed shortly after being diagnosed with hypertension. as part of his work-up he had a series of blood tests to screen for other risk factors:

Na^+	142 mmol/l
K^+	3.9 mmol/l
Urea	6.2 mmol/l
Creatinine	91 µmol/l

Fasting glucose	7.7 mmol/l

Total cholesterol	7.2 mmol/l

Based on the fasting glucose result you arrange a HbA1c:

HbA1c	31 mmol/mol (5.0%)

Which one of the following would explain the discrepancy between the HbA1c and fasting glucose levels?

	Vitamin B12 deficiency	7%
	Conn's syndrome	5%
🟥	Raised cholesterol level	18%
🟩	Sickle-cell anaemia	61%
	A history of alcohol excess	9%

The correct answer is **Sickle-cell anaemia**. HbA1c (glycated haemoglobin) is a measure of the average blood glucose levels over the past 2-3 months. In sickle-cell anaemia, red blood cells have an abnormally short lifespan due to their sickle shape, leading to a faster turnover of red blood cells. This means that there is less time for glucose to bind to haemoglobin, resulting in lower

HbA1c levels despite elevated fasting glucose levels.

Vitamin B12 deficiency can cause anaemia and peripheral neuropathy but does not directly affect HbA1c or fasting glucose levels. Vitamin B12 deficiency may lead to macrocytic (megaloblastic) anaemia, which can cause increased red cell turnover; however, this would not specifically explain the discrepancy between the HbA1c and fasting glucose levels observed in this case.

Conn's syndrome, also known as primary hyperaldosteronism, is characterised by excessive aldosterone production by the adrenal glands. This leads to sodium retention, potassium loss, and hypertension but does not directly affect HbA1c or fasting glucose levels.

Raised cholesterol level is a risk factor for cardiovascular disease and may be associated with type 2 diabetes mellitus; however, it does not directly affect HbA1c or fasting glucose levels and therefore would not explain the discrepancy between these two measurements in this patient.

Finally, **a history of alcohol excess** may lead to impaired glucose tolerance and contribute to the development of type 2 diabetes mellitus. However, alcohol consumption itself does not directly influence HbA1c or fasting glucose levels and thus would not explain the discrepancy observed in this case.

👍 👎 💬 Discuss (9) Improve

Next question

Glycosylated haemoglobin ★

Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus. HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration. The level of HbA1c therefore is dependent on:

- red blood cell lifespan
- average blood glucose concentration

A number of conditions can interfere with accurate HbA1c interpretation:

Lower-than-expected levels of HbA1c (due to reduced red blood cell lifespan)	**Higher-than-expected levels of HbA1c (due to increased red blood cell lifespan)**
Sickle-cell anaemia GP6D deficiency	Vitamin B12/folic acid deficiency Iron-deficiency anaemia

Lower-than-expected levels of HbA1c (due to reduced red blood cell lifespan)	Higher-than-expected levels of HbA1c (due to increased red blood cell lifespan)
Hereditary spherocytosis Haemodialysis	Splenectomy

HbA1c is generally thought to reflect the blood glucose over the previous '3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks. NICE recommend '*HbA1c should be checked every 3-6 months until stable, then 6 monthly*'.

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

HBA1c (%)	Average plasma glucose (mmol/l)	IFCC-HbA1c (mmol/mol)
5	5.5	
6	7.5	42
7	9.5	53
8	11.5	64
9	13.5	75
10	15.5	
11	17.5	
12	19.5	

From the above we can see that average plasma glucose = (2 * HbA1c) - 4.5

Next question

PassMedicine

Question 352 of 414 ✓

A 45-year-old female presented with symptoms of tremor, palpitations and weight loss. On assessment by her doctor there appeared to be neck swelling. Upon investigation by an ultrasound scan, a toxic multinodular goitre was demonstrated.

What would nuclear scintigraphy show in this case?

Absent uptake	1%
Diffuse uptake	14%
Increased uptake	21%
Patchy uptake	62%
Trace uptake	1%

In toxic multinodular goitre, nuclear scintigraphy reveals patchy uptake

Important for me Less important

Nuclear scintigraphy uses very small, tracer amounts of radioactive molecules to diagnose diseases involving bone, soft tissues and vessels.

Patchy uptake is seen with toxic multinodular goitre.

Diffusely and increased activity with a decreased background is seen in Graves disease.

Trace or absent uptake may indicate the presence of thyroiditis resulting in inflammation or destruction of thyroid tissue.

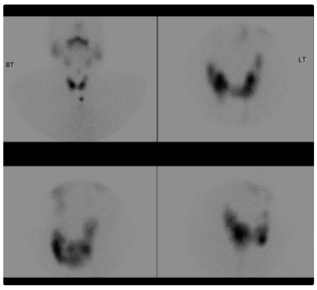
Discuss (2) Improve

Next question

Toxic multinodular goitre

Toxic multinodular goitre describes a thyroid gland that contains a number of autonomously functioning thyroid nodules resulting in hyperthyroidism.

Nuclear scintigraphy reveals patchy uptake.



The treatment of choice is radioiodine therapy.

Next question

Textbooks

High-yield textbook

Extended textbook

Score: **22.7%**

1 ✓
2 ✓
3 ✓
4 ✗

PassMedicine

Question 353 of 414 ✗

A 36-year-old woman who presented with a goitre is diagnosed with autoimmune thyroiditis. Which one of the following types of thyroid cancer is she predisposed to developing?

	Anaplastic	6%
🟩	Lymphoma	65%
🟥	Medullary	10%
	Follicular	9%
	Papillary	9%

Hashimoto's thyroiditis is associated with thyroid lymphoma

Important for me Less important

Discuss (1) Improve

Next question

Thyroid cancer

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

Main points

Type	Percentage	
Papillary	70%	Often young females - excellent prognosis

Type	Percentage	
Follicular	20%	
Medullary	5%	Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2
Anaplastic	1%	Not responsive to treatment, can cause pressure symptoms
Lymphoma	Rare	Associated with Hashimoto's thyroiditis

Management of papillary and follicular cancer
- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

Further information

Type	Notes
Papillary carcinoma	• Usually contain a mixture of papillary and colloidal filled follicles • Histologically tumour has papillary projections and pale empty nuclei • Seldom encapsulated • Lymph node metastasis predominate • Haematogenous metastasis rare
Follicular adenoma	• Usually present as a solitary thyroid nodule • Malignancy can only be excluded on formal histological assessment
Follicular carcinoma	• May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma. • Vascular invasion predominates • Multifocal disease raree
Medullary carcinoma	• C cells derived from neural crest and not thyroid tissue • Serum calcitonin levels often raised • Familial genetic disease accounts for up to 20% cases • Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis.

Type	Notes
Anaplastic carcinoma	- Most common in elderly females - Local invasion is a common feature - Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective.

Next question

Textbooks

High-yield textbook

Extended textbook

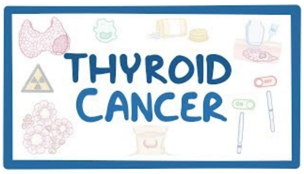
Links

British Thyroid Association 👍 3 👎 3

2014 Guidelines for the Management of Thyroid Cancer

Report broken link

Media



Thyroid cancer

Osmosis - YouTube 👍 20 👎 1

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Question 354 of 414 ✗

A 44-year-old woman presents with a 3-month history of nipple discharge with the appearance of milk. A systematic enquiry was otherwise unremarkable. She has a past medical history of schizophrenia for which she takes olanzapine. She also states that she smokes cannabis on a daily basis.

Blood results are as follows:

Thyroid stimulating hormone (TSH)	2.8 mU/L	(0.5-5.5)
Free thyroxine (T4)	4.2 pmol/L	(9.0 - 18)
Prolactin	165 ng/mL	(<25)
Oestradiol	22 pmol/L	(45 - 1461)
Lutenising hormone	1.6 IU/L	(2.1 - 103)
Follicular stimulating hormone	1.2 IU/L	(1.8 - 22.5)

What is the most likely cause of nipple discharge in this patient?

	Cannabis	4%
🟩	Non-functioning pituitary adenoma	29%
	Olanzapine	29%
🟥	Pregnancy	2%
	Prolactinoma	36%

The presence of an elevated prolactin level along with secondary hypothyroidism and hypogonadism is indicative of stalk compression is consistent with a non-functioning pituitary adenoma

Important for me Less important

The patient has hyperprolactinaemia with associated galactorrhoea. The causes of hyperprolactinaemia are wide. It is important to note that the patient also has secondary hypothyroidism (low T4 and inappropriately normal TSH) and hypogonadotrophic hypogonadism.

Non-functioning pituitary adenoma is correct. Non-functioning pituitary adenomas can result in panhypopituitarism due to infiltration of the normal pituitary tissue. Compression of the pituitary stalk can result in hyperprolactinaemia due to decreased transport of dopamine from the hypothalamus to the pituitary. Dopamine acts to suppress prolactin release. Thus a non-functioning pituitary adenoma accounts for all the biochemical abnormalities present in this case.

Cannabis is incorrect. Although there is weak evidence to show that cannabis can raise prolactin levels, it would not be expected to cause secondary hypothyroidism or hypogonadotrophic hypogonadism.

Olanzapine is incorrect. Although olanzapine is a well-known cause of hyperprolactinaemia and hypogonadotrophic hypogonadism, it is only very rarely associated with secondary hypothyroidism, making a non-functioning pituitary adenoma the more likely diagnosis.

Pregnancy is incorrect. Although pregnancy can result in hyperprolactinaemia, it is not associated with hypogonadotrophic hypogonadism or secondary hypothyroidism both of which are present in this case. Oestrogen levels increase steadily during pregnancy and reach their peak in the third trimester.

Prolactinoma is incorrect. The degree of hyperprolactinemia usually correlates with the size of prolactinoma. Although a macroprolactinoma causing compression of the pituitary gland remains within the differential diagnosis, this is less likely given the only very modest rise in prolactin levels. Macroprolactinomas are usually associated with serum prolactin levels >250 ng/ml. A serum prolactin level >500 ng/ml makes the diagnosis of macroprolactinoma almost certain.

👍 👎 Discuss (6) Improve

Next question

Pituitary adenoma

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people) but in most cases will never be found (asymptomatic) or are found as an incidental findings. They account for around 10% of adult brain tumours.

Pituitary adenomas can be classified according to:
- **size** (a microadenoma is <1cm and a macroadenoma is ≥1cm)
- **hormonal status** (a secretory/functioning adenoma produces an excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH-secreting and then ACTH-secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
    - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around the pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:
- a pituitary blood profile (including GH, prolactin, ACTH, FSH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:
- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of
- medical therapy:
    - prolactinomas are generally treated first-line with dopamine agonists (e.g., cabergoline or bromocriptine).
    - somatostatin analogues (e.g., octreotide, lanreotide) and GH receptor antagonists (e.g., pegvisomant) are used for GH-secreting adenomas
    - for ACTH-secreting adenomas, medical therapy may include cortisol synthesis inhibitors (e.g., ketoconazole, metyrapone) and neuromodulators like pasireotide
- transsphenoidal surgery

  - the primary treatment for most pituitary adenomas is transsphenoidal surgery, especially for non-functioning and ACTH- or GH-secreting adenomas
  - surgical intervention aims to remove the tumour mass, normalise hormone levels, and
  - non-functioning adenomas are generally diagnosed due to their compressive symptoms (e.g. visual problems) or hormone deficiencies - surgery is therefore the first-line treatment
- radiotherapy
  - indicated for residual or recurrent tumours post-surgery

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Patient.info 👍 7 👎 0

Pituitary tumours review

Report broken link

Score: **22.6%**

1 ✓
2 ✓
3 ✓

PassMedicine

Question 355 of 414 ✓

The fasting glucose for a patient is reported as follows:

Glucose (fasting)	**6.3 mmol/l**

What is the most likely underlying pathophysiological change?

	Beta-cell hyperplasia	5%
	Beta-cell atrophy	9%
	Muscle insulin resistance	16%
🟩	Hepatic insulin resistance	38%
	Adipose tissue insulin resistance	32%

Discuss (5) Improve

Next question

Prediabetes and impaired glucose regulation ★

Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. The term includes patients who have been labelled as having either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes. Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.

Terminology

- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

Identification of patients with prediabetes

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

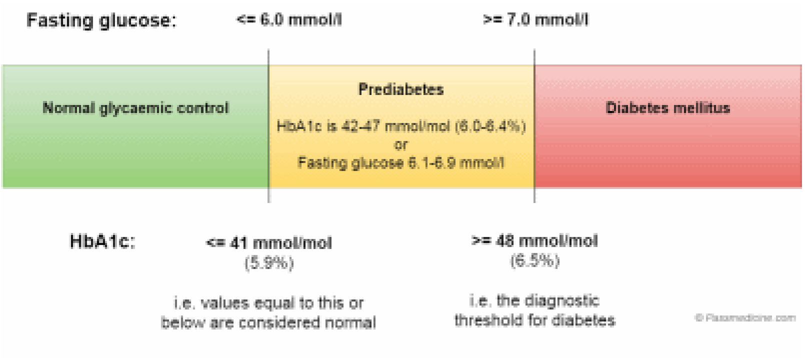
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
© Passmedicine.com

Diagram showing the spectrum of diabetes diagnosis

Management

- lifestyle modification: weight loss, increased exercise, change in diet
- at least yearly follow-up with blood tests is recommended
- NICE recommend metformin for adults at high risk '*whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme*'

Impaired fasting glucose and impaired glucose tolerance

There are two main types of IGR:

- impaired fasting glucose (IFG) - due to hepatic insulin resistance
- impaired glucose tolerance (IGT) - due to muscle insulin resistance
- patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Definitions

- a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)
- impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- people with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 2

2012 Preventing type 2 diabetes guidelines

Report broken link

Score: **22.8%**

1 ✓
2 ✓
3 ✓
4 ✗

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Question 356 of 414 ✓

A 50-year-old man presents with excessive thirst and constipation for the past 4 months. He wakes up several times in the night to urinate. He had a fracture of the right index finger two months ago after falling off from his bed. Physical examination shows no abnormalities. Ultrasound of the neck was arranged and showed bilateral parathyroid adenomas.

Laboratory blood investigations show:

Hb	140 g/L	Male: (135-180) Female: (115 - 160)
Platelets	190 * 10^9/L	(150 - 400)
WBC	5.2 * 10^9/L	(4.0 - 11.0)
Sodium	141 mmol/L	(135 - 145)
Potassium	4.5 mmol/L	(3.5 - 5.5)
Calcium	3 mmol/L	(2.2 - 2.6)
Phosphate	0.4 mmol/L	(0.74 - 1.4)
Albumin	30 g/L	(35 - 50)
Parathyroid hormone	9 pmol/L	(1.6 - 6.9)
25-Hydroxy Vitamin D	55 nmol/L	(>50)

Which of the following is the next best step in the definitive management of this patient's condition?

Cinacalcet	6%
Total parathyroidectomy	70%
Vitamin D supplementation	1%
Bisphosphonates	5%
Subtotal parathyroidectomy	19%

The definitive management of primary hyperparathyroidism is total parathyroidectomy

The definitive management of primary hyperparathyroidism is total parathyroidectomy

Important for me Less important

We have a case of primary hyperparathyroidism. Though the symptoms are non-specific, laboratory findings of high calcium and low phosphate along with the ultrasound showing adenomas make this diagnosis very likely. Also, past medical history shows a fracture after trivial trauma.

Cinacalcet is a calcimimetic which binds the calcium-sensing transmembrane receptor on the parathyroid gland making it more sensitive to serum calcium levels. The advantage of cinacalcet over vitamin D is that if itself does not induce hypercalcaemia. It is used in the management of primary hyperparathyroidism when surgery is not an option or declined.

The definitive management of primary hyperparathyroidism is total parathyroidectomy. Refer for surgery if primary hyperparathyroidism is confirmed and the patient has:
- Polydipsia, polyuria or constipation.
- Osteoporosis, fragility fracture or nephrolithiasis.
- Albumin-adjusted serum calcium is ≥ 2.85 mmol/L.

In any patient with suspected primary hyperparathyroidism, measure vitamin D levels and supplements offered if needed. Vitamin D causes increased absorption of calcium and phosphate from the gut, thereby has to be used with caution. It is be given safely in asymptomatic patients.

Primary hyperparathyroidism causes loss of bone mineral density and osteoporosis. Bisphosphonates inhibit the resorption of bone by osteoclasts and help in improving the osteoporosis. They do not have any direct effect on the parathyroid itself, so their use is limited to those patients who have an increased risk of fracture.

Check for albumin-adjusted serum calcium levels on two separate occasions and serum parathyroid levels. These results will help confirm the diagnosis and determine the next step in the management. After confirmation, the patient will need an assessment of comorbidities, eGFR and creatinine levels, DXA scan and ultrasound of the renal tract. The definitive management of primary hyperparathyroidism is total parathyroidectomy and not subtotal parathyroidectomy.

👍 👎 Discuss (4) Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism

- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':

- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II

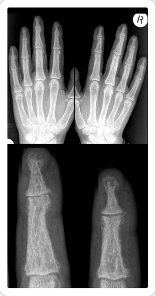
Investigations

- bloods
    - raised calcium, low phosphate
    - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
    - pepperpot skull
    - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic

  - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



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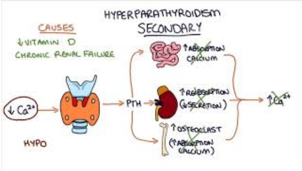
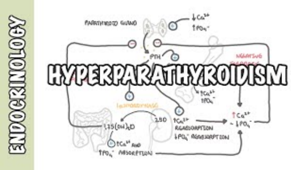

HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓VITAMIN D
CHRONIC RENAL FAILURE
↓Ca2+
HYPO
PTH
↑ABSORPTION CALCIUM
↑REABSORPTION (↓SECRETION)
↑OSTEOCLAST (↑ABSORPTION CALCIUM)
↑Ca2+

Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

PassMedicine

Question 357 of 414 ✗

You are reviewing a 22-year-old man who was recently admitted with a new diagnosis of type 1 diabetes, which presented as diabetic ketoacidosis.

He was discharged on a basal-bolus insulin regime and has had educational sessions with the diabetes specialist nurse.

Before his diagnosis, his health was good but is overweight with a BMI of 29.9kg/m^2.

At your clinic, you discuss his insulin regime, diet and lifestyle factors, and sick day rules.

The patient wonders if there is any other medication that would benefit him at this stage.

What drug may offer him benefit for his glycaemic control?

	Alogliptin	7%
	Empagliflozin	10%
	Gliclazide	7%
🟩	Metformin	57%
🟥	Semaglutide	19%

Patients with type I diabetes and a BMI > 25 should be considered for metformin in addition to insulin

Important for me Less important

This patient is a newly diagnosed type 1 diabetic and the mainstay of his management will be insulin. That said, NICE recommend the use of **metformin** for patients with type 1 diabetes who are overweight with a BMI of 25kg/m^2 or over, so this is the correct answer in this case.

Metformin increases insulin sensitivity and has benefits for overall cardiovascular health and can allow lower doses of insulin to be administered.

The other drugs mentioned are not used in type 1 diabetes so are not correct.

Alogliptin and **gliclazide** work by increasing the endogenous production of insulin, so this will not work in type 1 diabetes as there is very little endogenous insulin produced., therefore they are both incorrect.

Empagliflozin is incorrect. This is an SGLT-2 inhibitor and is not used in the treatment of type 1 diabetes as there is a significant risk of developing diabetic ketoacidosis which is a particular concern in this case given the recent episode of this.

Semaglutide is not currently licensed for type 1 diabetes so is incorrect. There has been some recent research indicating it may be a potential treatment option in the future.

👍 👎 💬 Discuss (2) Improve

Next question

Diabetes mellitus: management of type 1 ★

The long-term management of type 1 diabetics is an important and complex process requiring the input of many different clinical specialties and members of the healthcare team. A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

NICE released guidelines on the diagnosis and management of type 1 diabetes in 2015. We've only highlighted a very select amount of the guidance here which will be useful for any clinician looking after a patient with type 1 diabetes.

HbA1c
- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

Self-monitoring of blood glucose
- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

Blood glucose targets

- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

Type of insulin

- offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

Metformin

- NICE recommend considering adding metformin if the BMI >= 25 kg/m^2

Next question

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NICE 👍 4 👎 2

2015 Type 1 diabetes in adults: diagnosis and management

NICE 👍 3 👎 2

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Question 358 of 414 ✗

A 20-year-old male patient presents to the endocrine clinic with delayed-onset puberty. His history revealed a cleft palate as a child which had been repaired successfully. On direct questioning, he revealed he had anosmia but was told this was due to a minor head injury aged 3. On examination, he was 1.82 metres tall, had sparse pubic hair and small volume testes (Tanner staging grade 1).

Blood results revealed:

FSH	2 IU/L	(1-7)
LH	2 IU/L	(1-8)
Testosterone	230 ng/dL	(280-1100)

What is the most likely cause of this patients condition?

	Constitutional developmental delay	1%
🟥	Empty sella syndrome	2%
🟩	Kallman's syndrome	74%
	Klinefelter's syndrome	21%
	Turner's syndrome	2%

Kallman's syndrome - LH & FSH low-normal and testosterone is low

Important for me Less important

The minor head injury is unlikely to have caused his anosmia. The combination of anosmia and cleft palate along with the blood tests suggesting hypogonadotropic hypogonadism points towards Kallmann's syndrome as the unifying diagnosis. This is X-linked inherited.

The abnormal blood tests and age of presentation make constitutional developmental delay less likely.

Empty sella syndrome is a condition whereby the sella turcica, the area of the brain in which the pituitary sits is found to be empty and replaced by cerebrospinal fluid. This condition can be asymptomatic but can also present with signs of hypopituitarism. As this patient has the additional features of anosmia and cleft palate, empty sella syndrome is less likely in this patient.

Klinefelter's syndrome presents with tall stature, gynaecomastia and a small penis/ testes. Blood tests would reveal raised gonadotropins and low testosterone. It has a karyotype of XXY. This patient has low FSH and LH and therefore ruling out Klinefelter's syndrome.

Turner's syndrome only occurs in females and is characterised by short stature and a webbed neck. It has a karyotype of XO.

👍 👎 Discuss (8) Improve

Next question

Kallmann's syndrome ★

Kallmann's syndrome is a recognised cause of delayed puberty secondary to hypogonadotropic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallmann's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty.

Features
- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above-average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

Management
- testosterone supplementation
- gonadotrophin supplementation may result in sperm production if fertility is desired later in life

Next question

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← Question 359 of 414 ✗ →

A 63-year-old woman with a history of type 2 diabetes is being reviewed by her general practitioner.

She is currently taking metformin 1g twice daily. She also takes lisinopril for hypertension.

Her latest HbA1c is as follows:

HbA1c	58 mmol/L	(<42)

After further discussion, she has agreed to add a second anti-diabetic drug to her treatment regimen. She has been advised that side-effects can include weight gain, hypoglycaemia and gastrointestinal upset.

What is the mechanism of action of this drug?

	Activation of peroxisome proliferator activated receptor gamma (PPAR gamma)	8%
🟩	Binding to K_{ATP} channels on pancreatic beta cell membrane	78%
	Activation of glucagon-like-peptide-1 (GLP-1) receptor	5%
🟥	Inhibition of sodium-glucose co-transporter 2 (SGLT-2)	5%
	Inhibition of dipeptidyl peptidase 4 (DPP-4)	5%

Sulfonylureas - bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells

Important for me Less important

While this patient could potentially be offered a number of oral anti-diabetic medications as an add-on therapy for her type 2 diabetes, the side-effects that she has been counselled about suggest that a sulphonylurea has been commenced.

Sulphonylureas exert their effect by binding to K_{ATP} channels on the pancreatic beta-cell membrane to stimulate endogenous insulin secretion. This explains the commonly reported side-effects of weight gain (as insulin is an anabolic hormone) and hypoglycaemia.

Activation of peroxisome proliferator-activated receptor-gamma (PPAR gamma) is the principal mechanism of action of thiazolidinediones (glitazones), which results in increased insulin sensitivity. They can cause weight gain and fluid retention, but do not cause hypoglycaemia.

Glucagon-like-peptide-1 (GLP-1) analogues include drugs such as liraglutide. These tend to reduce weight by delaying gastric emptying and reducing hunger and do not cause hypoglycaemia.

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors (such as dapagliflozin) are also an effective treatment for type 2 diabetes but do not cause weight gain or hypoglycaemia. Conversely, the glycosuric effect can promote weight loss.

Inhibition of dipeptidyl peptidase 4 (DPP-4), such as sitagliptin, tend to be weight neutral and do not cause hypoglycaemia. They reduce the breakdown of incretins and hence stimulate endogenous insulin release in a glucose-dependent fashion.

Discuss (1) Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects
- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects
- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

Next question

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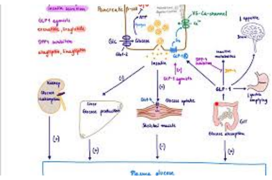

Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

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← Question 360 of 414 ✓ →

Which one of the following is the most common non-iatrogenic cause of Cushing's syndrome?

Ectopic ACTH production	21%
Adrenal adenoma	42%
Micronodular adrenal dysplasia	6%
Adrenal carcinoma	2%
Pituitary tumour	30%

The correct answer is **Pituitary tumour**. This condition, also known as Cushing's disease, is the most common non-iatrogenic cause of Cushing's syndrome. It accounts for about 70% of cases not related to medication use. The pathogenesis involves a pituitary adenoma secreting excess adrenocorticotropic hormone (ACTH), which stimulates the adrenal glands to produce an overabundance of cortisol.

Ectopic ACTH production is another cause of Cushing's syndrome but it is less common than pituitary tumours. Ectopic ACTH production usually results from small-cell lung cancer or bronchial carcinoids and leads to high levels of cortisol. However, this cause accounts for only about 10% of non-iatrogenic cases.

Adrenal adenoma can indeed lead to Cushing's syndrome but it is also less common than pituitary tumours. Adrenal adenomas are benign neoplasms that can secrete excess cortisol independently from ACTH stimulation, leading to hypercortisolism. They account for around 15-20% of endogenous cases.

Micronodular adrenal dysplasia, a rare form of bilateral adrenal hyperplasia, causes less than 1% of endogenous Cushing's syndrome cases. In micronodular adrenal dysplasia, multiple small nodules in the adrenal glands produce excess cortisol.

Lastly, **Adrenal carcinoma** is a very rare cause of Cushing's syndrome. These malignant tumours can autonomously produce high levels of cortisol but are very infrequent compared to other causes.

Discuss (11) | Improve

Next question

Cushing's syndrome: causes

It should be noted that exogenous causes of Cushing's syndrome (e.g. glucocorticoid therapy) are far more common than endogenous ones.

ACTH dependent causes

- Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
- ectopic ACTH production (5-10%): e.g. small cell lung cancer is the most common causes

ACTH independent causes

- iatrogenic: steroids
- adrenal adenoma (5-10%)
- adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma
- micronodular adrenal dysplasia (very rare)

Pseudo-Cushing's

- mimics Cushing's
- often due to alcohol excess or severe depression
- causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- insulin stress test may be used to differentiate

Next question

Textbooks

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Links

DermNet NZ 👍 1 👎 2

Side-effects of systemic steroids

Report broken link

Media

CUSHING SYNDROME

Cushing syndrome

Osmosis - YouTube 👍 21 👎 2

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Score: **23.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗

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← Question 361 of 414 ✕ ⚐ →

A 72-year-old man presents to the emergency department with confusion. His history includes hypertension, for which he is on bendroflumethiazide. He consumes 30 units of alcohol per week.

On examination, he appears confused. A CT head scan is normal.

Blood tests:

Na^+	112 mmol/L	(135 - 145)

He receives 3L of normal saline to correct the sodium imbalance.

Blood tests taken 24 hours later show:

Na^+	144 mmol/L	(135 - 145)

Three days post-correction, the man develops spastic quadriparesis, pseudobulbar palsy, and emotional lability.

What is the underlying pathophysiology most likely responsible for these developments?

🟩	Astrocyte apoptosis	73%
🟥	Astrocyte paligenosis	16%
	Focal immune cell infiltration	3%
	Thiamine deficiency	7%
	Vascular occlusion	2%

Osmotic demyelination syndrome develops secondary to astrocyte apoptosis

Important for me Less important

Astrocyte apoptosis is the correct answer. The patient presents with confusion, which is likely due to hyponatraemia resulting from treatment with bendroflumethiazide. The hyponatraemia has been corrected too swiftly, with a rise of 32 mmol/L in 24 hours, exceeding the recommended increment of less than 12mmol/L per day (ideally between 4-6 mmol/L). Three days later, the patient develops spastic quadriparesis, pseudobulbar palsy, and emotional lability. These symptoms are indicative of central pontine myelinolysis in this context, also known as osmotic demyelination syndrome. This condition is believed to be caused by astrocyte apoptosis. Chronic hyponatraemia leads to the depletion of osmotically active organic osmolytes such as myoinositol, glutamate, and glutamine from astrocytes, which serve to protect against cerebral oedema. During rapid correction of hyponatraemia, these organic osmolytes cannot be replenished quickly enough as brain volume decreases. Consequently, dehydration induces apoptosis or other forms of injury in astrocytes and oligodendrocytes, leading to demyelination that is typically irreversible.

Astrocyte paligenosis is incorrect. Paligenosis represents essentially the opposite process to apoptosis; it enables cells to avoid death through mechanisms including the key protein mTORC1. In this scenario involving astrocyte cell death as a primary mechanism for osmotic demyelination syndrome, paligenosis does not provide an appropriate explanation.

Focal immune cell infiltration is incorrect. While spastic paraparesis may occur in conditions like multiple sclerosis due to focal immune cell infiltration causing demyelination, the history of sodium overcorrection followed by acute clinical deterioration points towards osmotic demyelination syndrome as a more probable diagnosis.

Thiamine deficiency is incorrect. Although excessive alcohol consumption places the patient at risk for Wernicke's encephalopathy'stemming from thiamine deficiency'this disorder typically manifests with ataxia, nystagmus and ophthalmoplegia rather than spastic quadriparesis and pseudobulbar palsy.

Vascular occlusion is incorrect. A brainstem stroke remains an important consideration when differentiating causes of neurological symptoms but given the clinical presentation and timing following rapid sodium correction, osmotic demyelination syndrome secondary to swift hyponatraemia management emerges as a more likely cause in this case.

👍 👎 Discuss Improve

Next question

Hyponatraemia: treatment ★

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:

- duration of hyponatremia: is it acute or chronic?
  - acute: develops over a period of < 48 hours
  - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
  - mild: 130-134 mmol/L
  - moderate: 120-129 mmol/L
  - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
  - patients with mild hyponatraemia may be symptomatic
  - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
  - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
  - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
  - euvolemic hyponatraemia: SIADH
  - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients

- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected

- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
  - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
  - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected

- fluid restrict to 500-1000 mL/day

- consider medications:
  - demeclocycline
  - vaptans (see below)

If a hypervolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):
- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)
- can occur due to over-correction of severe hyponatremia
- pathophysiology:
  - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
  - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema

  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

Textbooks

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Links

Royal College of Physicians 👍 15 👎 3

2017 Hyponatraemia â€“ presentations and management

Report broken link

Score: **23%**

1 ✓
2 ✓

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Question 362 of 414 ✗

A 23-year-old woman is admitted to the intensive care unit following an episode of diabetic ketoacidosis. On admission her Glasgow coma scale was 7/15. Collateral history revealed long-standing type 1 diabetes mellitus with poor glycaemic control.

Arterial blood gases:

pH	7.12
paCO2	3.1 kPa
paO2	12.2 kPa
HCO3	3 mmol/l

Capillary Glucose: 33mmol/L

Urine dip:

glucose	+++
ketones	+++
protein	-
nitrites	-
Leucocyte esterase	-

The patient was intubated and successfully treated with intravenous fluids, insulin and venous thromboembolism prophylaxis.

On discharge her GP undertook a routine screen of blood tests.

Which of the following thyroid function tests results would be in keeping with her presentation?

TSH - high, T4 - Low, T3 high	9%
TSH - high, T4 - normal, T3 normal	17%
TSH - low, T4 - Low, T3 high	14%

🟥 TSH - low, T4 - normal, T3 normal	16%
🟩 TSH - normal, T4 - Low, T3 low	44%

Sick euthyroid syndrome is a reversible state of abnormal thyroid function tests due to a non-thyroidal illness, without pre-existing hypothalamic-pituitary or thyroid gland dysfunction. By definition, after recovery of the non-thyroidal illness, thyroid function tests should revert back to normal.

Causes of sick euthyroid include: myocardial infarctions, starvation, burns, trauma, surgery, malignancy, diabetic ketoacidosis, any organ failure and inflammatory conditions.

The pathology postulated is the down regulation of type 1 deiodinase, reducing the peripheral conversion of T4 to T3 and thus reducing the basal metabolic rate during periods of stress. Upregulation of type 3 deiodinase to inactive (reverse) T3 also aids to reducing basal metabolic rate.

Discuss (8) Improve

Next question

Sick euthyroid syndrome

In sick euthyroid syndrome (now referred to as non-thyroidal illness) it is often said that everything (TSH, thyroxine and T3) is low. In the majority of cases however the TSH level is within the >normal range (inappropriately normal given the low thyroxine and T3).

Changes are reversible upon recovery from the systemic illness and hence no treatment is usually needed.

Next question

PassMedicine

Question 363 of 414 ✗

A 65-year-old woman presents to the Outpatients department complaining of urinary incontinence. She reveals that over the past year, she has had episodes where she has lost continence of her bladder in public. This has happened most frequently when she has coughed, sneezed or laughed. Otherwise, she tends not to have trouble getting to the toilet in time, and is generally fit and well in herself.

Her past medical history includes hypercholesterolaemia, for which she takes atorvastatin 40mg ON. She has two children, who were delivered vaginally without any perinatal complications. Her body mass index is 29kg/m^2.

She has read on the internet about the importance of pelvic floor exercises, and has been persevering with these for the last six months. In spite of this, her symptoms have persisted. She is reluctant to undergo surgical intervention unless absolutely necessary.

What is the most appropriate next step in the management of this patient's incontinence?

	Colposuspension	3%
	Mirabegron	10%
🟩	Duloxetine	73%
🟥	Oxybutynin	12%
	Tolterodine	2%

Duloxetine may be used in patients with stress incontinence who don't respond to pelvic floor muscle exercises and decline surgical intervention

Important for me Less important

This patient has presented with classic features of stress incontinence - i.e. incontinence provoked by sudden increases in intra-abdominal pressure, such as when sneezing, laughing or coughing. Her sex, age, raised BMI and history of previous vaginal deliveries are all risk factors for the development of stress incontinence. The first-line intervention for confirmed or presumed stress incontinence is pelvic floor exercises. However, as this patient has tried these for a substantial period of time without symptomatic improvement, further interventions are necessary. As she has expressed a strong wish to avoid surgical intervention, which may otherwise be indicated at this stage, the most appropriate management option is duloxetine, which can enhance contraction of the urethral sphincter.

Colposuspension would be a sensible management option for a patient with stress incontinence who was more amenable to a surgical procedure.

Mirabegron is a beta-3 adrenergic receptor agonist used in the management of urge incontinence in patients for whom antimuscarinics are contraindicated.

Oxybutynin and tolterodine are both immediate-release antimuscarinics used in the management of urge incontinence.

👍 👎 Discuss (1) Improve

Next question

Urinary incontinence

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification

- overactive bladder (OAB)/urge incontinence
    - due to detrusor overactivity
    - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
    - comorbid physical conditions impair the patient's ability to get to a bathroom in time

  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
  - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
  - a combined noradrenaline and serotonin reuptake inhibitor
  - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Next question

PassMedicine

Question 364 of 414 ✗

A 68-year-old man attends his GP surgery for his chronic disease annual review following on from recent blood tests.

His past medical history includes hypertension, polymyalgia rheumatica and type 2 diabetes mellitus.

He regularly takes amlodipine, bendroflumethiazide, prednisolone on a reducing regimen, sitagliptin and metformin.

Hb	142 g/L	Male: (135-180) Female: (115 - 160)
Platelets	270 * 10^9/L	(150 - 400)
WBC	12.8 * 10^9/L	(4.0 - 11.0)
Neuts	10.6 * 10^9/L	(2.0 - 7.0)

Which is his medications is the most likely cause of his raised neutrophil count?

Amlodipine	1%
Bendroflumethiazide	6%
🟥 Metformin	1%
🟩 Prednisolone	86%
Sitagliptin	5%

Glucocorticoid treatment can induce neutrophilia

Important for me Less important

Amlodipine and bendroflumethiazide can cause leucopenia, not neutrophilia.

Sitagliptin and metformin don't affect leukocytes.

Prednisolone can cause neutrophilia through:

- Demargination of neutrophils via the endovascular lining

- Demargination of neutrophils via the endovascular lining.
- Delayed migration of neutrophils into tissue.
- Release of immature neutrophils from bone marrow.

During bacterial infection, there is an increased 'left shift' seen on microscopy. In 'left shift' neutrophils are produced and released from the bone marrow at an equal rate to their consumption in the circulation.

With steroid use, 'left shift' generally does not occur due to increased production and release of neutrophils from the bone marrow but no neutrophil consumption.

👍 👎 Discuss Improve

Next question

Corticosteroids: side-effects

Glucocorticoid side-effects

- endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, hyperlipidaemia
- Cushing's syndrome: moon face, buffalo hump, striae
- musculoskeletal: osteoporosis, proximal myopathy, avascular necrosis of the femoral head
- immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis
- psychiatric: insomnia, mania, depression, psychosis
- gastrointestinal: peptic ulceration, acute pancreatitis
- ophthalmic: glaucoma, cataracts
- dermatological: acne
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Next question

PassMedicine

Question 365 of 414 ✗

A 49-year-old woman is investigated for thyrotoxicosis. On examination she is noted to have a goitre containing multiple irregular nodules. Nuclear scintigraphy with technetium 99m reveals patchy uptake. What is the treatment of choice?

🟥 Corticosteroids	3%
🟩 Radioiodine	41%
Block-and-replace regime	11%
Surgery	29%
Anti-thyroid drug titration regime	16%

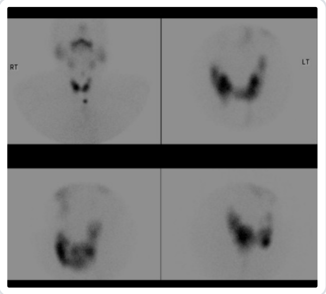
Discuss (8) Improve

Next question

Toxic multinodular goitre

Toxic multinodular goitre describes a thyroid gland that contains a number of autonomously functioning thyroid nodules resulting in hyperthyroidism.

Nuclear scintigraphy reveals patchy uptake.



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Question 366 of 414 ✗

A 55-year-old female with a large uterine fibroid that was planned to be removed by her gynaecologist was referred to the haematology clinic as her preoperative blood results showed polycythaemia.

Her past medical history includes type 2 diabetes mellitus (T2DM) and hypertension, for which she is taking metformin, insulin and enalapril. She drinks alcohol occasionally and smokes 3 cigarettes daily for 2 years. On examination, she is well and fit with no clinically detected abnormalities.

Investigations reveal the following:

Hb	190 g/L	(115 - 160)
Platelets	350 * 10^9/L	(150 - 400)
WBC	10 * 10^9/L	(4.0 - 11.0)

Bilirubin	11 µmol/L	(3 - 17)
ALP	100 u/L	(30 - 100)
ALT	35 u/L	(3 - 40)
Albumin	40 g/L	(35 - 50)

Urea	6 mmol/L	(2.0 - 7.0)
Creatinine	95 µmol/L	(55 - 120)

Which of the following is the most likely cause of her polycythaemia?

	Cigarette smoking	26%
	Enalapril	3%
	Insulin	2%
🟥	Metformin	2%
🟩	Uterine fibroid	66%

Uterine fibroids may rarely be associated with secondary polycythaemia due to autonomous production of erythropoietin

Important for me Less important

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary. Excessive erythropoietin from uterine fibroids or some other tumours (e.g. cerebellar haemangioma, hypernephroma, hepatoma) can lead to secondary polycythaemia.

Insulin, metformin, enalapril are not considered causes of polycythaemia. Drugs associated with secondary polycythaemia include exogenous erythropoietin, anabolic steroids and testosterone replacement therapy. Diuretics can cause an apparent polycythaemia (due to plasma volume contraction) rather than a true increase in red cell count.

Long-term smoking can cause chronic obstructive pulmonary disease and chronic hypoxaemia, which can lead to secondary polycythaemia. But this is unlikely in our patient given her relatively low pack-year history.

Discuss (5) Improve

Next question

Uterine fibroids

Fibroids are benign smooth muscle tumours of the uterus. They are thought to occur in around 20% of white and around 50% of black women in the later reproductive years.

Associations
- more common in Afro-Caribbean women
- rare before puberty, develop in response to oestrogen

Features
- may be asymptomatic
- menorrhagia
  - may result in iron-deficiency anaemia
- bulk-related symptoms
  - lower abdominal pain: cramping pains, often during menstruation
  - bloating
  - urinary symptoms, e.g. frequency, may occur with larger fibroids
- subfertility

- rare features:
    - polycythaemia secondary to autonomous production of erythropoietin

Diagnosis

- transvaginal ultrasound

Management

Asymptomatic fibroids

- no treatment is needed other than periodic review to monitor size and growth

Management of menorrhagia secondary to fibroids

- levonorgestrel intrauterine system (LNG-IUS)
    - useful if the woman also requires contraception
    - cannot be used if there is distortion of the uterine cavity
- NSAIDs e.g. mefenamic acid
- tranexamic acid
- combined oral contraceptive pill
- oral progestogen
- injectable progestogen

Treatment to shrink/remove fibroids

- medical
    - GnRH agonists may reduce the size of the fibroid but are typically used more for short-term treatment due to side-effects such as menopausal symptoms (hot flushes, vaginal dryness) and loss of bone mineral density
    - ulipristal acetate has been in the past but not currently due to concerns about rare but serious liver toxicity
- surgical
    - myomectomy: this may be performed abdominally, laparoscopically or hysteroscopically
    - hysteroscopic endometrial ablation
    - hysterectomy
- uterine artery embolization

Prognosis and complications

Fibroids generally regress after the menopause.

Some of the complications such as subfertility and iron-deficiency anaemia have been mentioned previously.

Other complications

- red degeneration - haemorrhage into tumour - commonly occurs during pregnancy

Next question

Textbooks

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Links

Clinical Knowledge Summaries 👍 0 👎 0

Fibroids guidelines

Report broken link

Media

UTERINE FIBROID
OSMOSIS.org

Uterine fibroids

Osmosis - YouTube 👍 6 👎 1

Report broken media

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Question 367 of 414 ✗

A 68-year-old female with a background of stage four chronic kidney disease (CKD) presents with the following blood results to the nephrology clinic. She has had progressive CKD over many years following a diagnosis of IgA nephropathy in her third decade.

PTH	19.1 pmol/l (1.05 - 6.83)
Adjusted calcium	2.84 mmol/l (2.1-2.6)

What endocrine abnormality is she most likely to have given her background?

🟩	Tertiary hyperparathyroidism	52%
	Secondary hyperparathyroidism	29%
	Multiple endocrine neoplasia 1 (MEN1)	5%
	Pseudohypoparathyroidism	2%
🟥	Primary hyperparathyroidism	13%

The correct answer is tertiary hyperparathyroidism. The PTH level is inappropriate given the high calcium level indicating autonomous hypersecretion of PTH. Although such results could be possible with primary hyperparathyroidism, the long history of renal impairment points towards tertiary hyperparathyroidism as the hypertrophied parathyroid glands no longer respond to serum calcium levels. Tertiary hyperparathyroidism occurs after long term secondary hyperparathyroidism.

Primary hyperparathyroidism

- PTH over-secretion usually from a parathyroid adenoma
- both PTH and calcium are elevated
- surgery to remove the adenoma is the most effective treatment
- conservative measures such as bisphosphonates can be used

Secondary hyperparathyroidism

- occurs in chronic kidney disease typically
- can be secondary to vitamin D deficiency

- PTH released due to low calcium, high phosphate and lack of vitamin D activation by diseased kidneys
- PTH level high with calcium levels being low or normal
- medical management primarily: phosphate binders, calcium and vitamin D supplementation

Tertiary hyperparathyroidism

- autonomous hypersecretion of PTH due to hypertrophied parathyroid glands
- occurs after a period of long standing secondary hyperparathyroidism
- treatment involves parathyroidectomy

Pseudohypoparathyroidism is caused by PTH resistance and is associated with low calcium and high PTH levels. MEN1 is a rare hereditary disorder involving multiple types of endocrine tissue neoplasia.

👍 👎 Discuss (5) Improve

Next question

Hypercalcaemia: causes ★

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
  - PTHrP from the tumour e.g. squamous cell lung cancer
  - bone metastases
  - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include

- sarcoidosis
  - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome

- drugs:
  - thiazides
  - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
  - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

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Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€“ presentation and management

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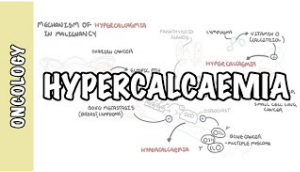
Media


ONCOLOGY
HYPERCALCAEMIA
MECHANISM OF HYPERCALCAEMIA IN MALIGNANCY

Hypercalcemia in malignancy

Armando Hasudungan - YouTube 👍 19 👎 2

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Question 368 of 414 ✓

A 45-year-old woman who has a history of Graves' disease presents with visual problems. She is known to have Graves' ophthalmopathy and does not currently smoke. Her most recent thyroid function tests are shown below:

Free T4	15 pmol/l
TSH	1.6 mu/l

Which one of the following features is the strongest indicator of the need for urgent ophthalmology review?

Sensitivity of eyes to light	3%
Diplopia	25%
Troublesome eyelid retraction	19%
Awareness of change in intensity or quality of colour vision	47%
Erythema of the conjunctiva	6%

The other symptoms/signs indicate the need for non-urgent review by an opthalmologist. Please see the EUGOGO guidelines for more details.

Discuss (3) Improve

Next question

Thyroid eye disease

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation

- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eyelids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

Management

- smoking cessation
- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

Complications

Exposure keratopathy

- this is the most common complication of thyroid eye disease
- due to eyelid retraction and proptosis (exophthalmos) → cornea becomes excessively exposed, disrupting the normal tear film → dryness, irritation, and corneal ulceration
- symptoms include foreign body sensation, pain, and photophobia
- in severe cases, it can lead to corneal scarring and vision impairment.

Optic neuropathy

- one of the most serious complications of thyroid eye disease
- occurs when enlarged extraocular muscles compress the optic nerve at the apex of the orbit → a reduction in visual acuity, colour vision deficits, and visual field defect
- it requires urgent medical intervention to prevent permanent vision loss.

Strabismus and diplopia

- fibrosis and enlargement of the extraocular muscles can result in restrictive strabismus → misalignment of the eyes → double vision (diplopia)
- this not only affects visual function but can also significantly impair the quality of life.

Monitoring patients with established thyroid eye disease

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

Next question

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Links

Consensus Statement of the European Group on Graves' Orbitopathy 👍 2 👎 1

Management of Graves' Orbitopathy

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Question 369 of 414

A 64-year-old woman presents with a painless lump in her neck. She reports that it has been gradually enlarging for the past 2 months. She denies any fevers, night sweats or weight loss.

She has a history of Hashimoto's thyroiditis and has been on levothyroxine daily for the past 30 years.

On examination, she is clinically euthyroid with a pulse rate of 76/min. Neck examination reveals a non-tender thyroid gland with a firm and smooth 3cm left thyroid lobe mass. Her thyroid-stimulating hormone (TSH) is within the normal range.

What is the most likely diagnosis?

Anaplastic thyroid carcinoma	10%
Mucosa-associated lymphoid tissue (MALT) lymphoma	75%
Pyramidal thyroid lobe	6%
Reidel's thyroiditis	7%
Toxic adenoma	3%

Hashimoto's thyroiditis is associated with the development of MALT lymphoma

Important for me Less important

The presence of a new thyroid mass on a background of longstanding Hashimoto's thyroiditis should arouse the suspicion of mucosa-associated lymphoid tissue (MALT) lymphoma.

The thyroid gland is normally devoid of lymphocytic tissue. However in chronic inflammatory conditions such as Hashimoto's thyroiditis, malignancy can arise in this setting. It tends to occur more commonly in females between 65 and 75 years old, although it is rare.

Thyroid MALT lymphoma tends to follow an indolent course and often presents as a neck lump without typical 'B' symptoms such as fever, night sweats and weight loss. Some patients may report compression symptoms such as dysphagia and dyspnoea.

The diagnosis is confirmed via an ultrasound scan and fine-needle aspiration cytology.

Anaplastic thyroid carcinoma is a rare subtype of thyroid cancer which manifests as a rapidly enlarging neck mass, usually with compression symptoms. It is not associated with Hashimoto's thyroiditis.

Riedel's thyroiditis is characterised by the replacement of the normal thyroid parenchyma by dense fibrotic tissue that extends beyond the thyroid capsule, resulting in a hard 'woody' thyroid gland and compression symptoms.

The pyramidal thyroid lobe is a normal anatomic variant seen in 10-30% of the population, seen as a third thyroid lobe arising from the isthmus. It is generally asymptomatic and found incidentally on ultrasound.

Toxic adenomas are functioning thyroid nodules that autonomously secrete thyroxine, and usually manifest in symptoms of thyrotoxicosis.

👍 | 👎 | Discuss (1) | Improve

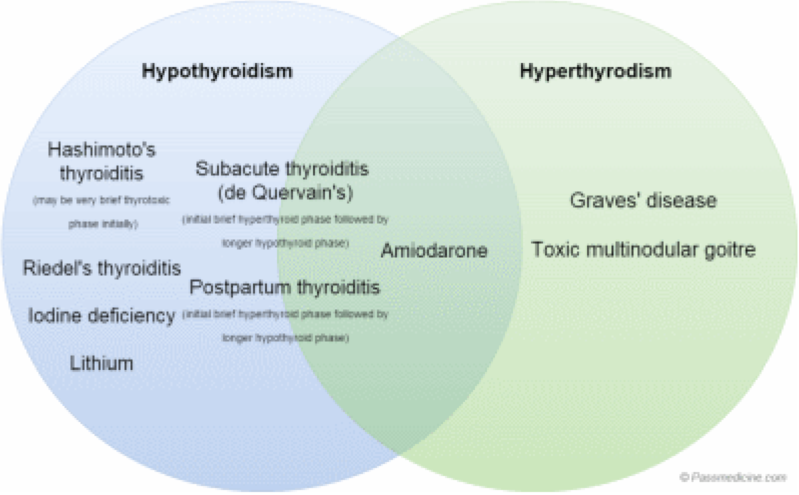
Next question

Hashimoto's thyroiditis ★

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features
- features of hypothyroidism
- goitre: firm, non-tender
- anti-thyroid peroxidase (TPO) and also anti-thyroglobulin (Tg) antibodies

Associations
- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of MALT lymphoma


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
Graves' disease
Toxic multinodular goitre
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Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

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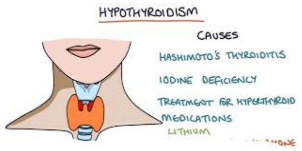
HYPOTHYROIDISM
CAUSES
HASHIMOTO'S THYROIDITIS
IODINE DEFICIENCY
TREATMENT FOR HYPERTHYROID
MEDICATIONS
LITHIUM

Hypothyroidism and Hashimoto's Thyroiditis: Visual Explanation for Students

Zero To Finals - YouTube 👍 18 👎 1

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Question 370 of 414 ✗

What is the mechanism of action of thiazolidinediones?

PPAR-gamma receptor antagonist	28%
PPAR-alpha receptor antagonist	14%
PPAR-alpha receptor agonist	14%
PPAR-gamma receptor agonist	40%
Increases endogenous insulin secretion	4%

Glitazones are agonists of PPAR-gamma receptors, reducing peripheral insulin resistance

Important for me Less important

Discuss (5) Improve

Next question

Thiazolidinediones

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. It's natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects
- weight gain
- liver impairment: monitor LFTs

- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

Next question

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Links

NICE 👍 1 👎 0

2022 Type 2 diabetes guidelines

Report broken link

Score: **22.7%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗

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Question 371 of 414 ✓

A 69-year-old woman was admitted with a seizure. This was her presentation and has never had seizures before. She has advanced dementia and is currently in a care home. The nursing staff report chronically poor oral intake of both food and fluid.

Blood tests were performed to identify a possible cause for her seizures.

Na^+	119 mmol/L	(135 - 145)
K^+	3.4 mmol/L	(3.5 - 5.0)
Bicarbonate	16 mmol/L	(22 - 29)
Urea	13 mmol/L	(2.0 - 7.0)
Creatinine	177 µmol/L	(55 - 120)

What would be the most appropriate management in this case?

Intravenous dextrose	1%
Intravenous hypertonic saline	78%
Intravenous normal saline	17%
Intravenous plasma-lyte	1%
Intravenous 1.28% sodium bicarbonate	2%

Hypertonic saline is usually indicated in patients with acute, severe, symptomatic hyponatraemia (< 120 mmol/L)

Important for me Less important

Hypertonic saline is usually indicated in patients with severe hyponatraemia (< 120 mmol/L) which the situation here and the most likely cause for her seizure.

Intravenous normal saline would be appropriate to help with hydration and hyponatraemia but in this case, given the severity of the situation, hypertonic saline is indicated.

Intravenous plasma-lyte is an isotonic solution of electrolytes and whilst it would help hydrate the patient would not add a significant benefit in correcting the hyponatraemia.

Intravenous 1.28% sodium bicarbonate would not be appropriate in this case given that it would not be helping to treat the main underlying issue of hyponatraemia which is the most likely cause of her seizure.

Intravenous dextrose would not be appropriate in this case given that it would not be helping to treat the main underlying issue of hyponatraemia and is often utilised in situations of hypernatraemia.

👍 👎 Discuss (7) Improve

Next question

Hyponatraemia: treatment

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:

- duration of hyponatremia: is it acute or chronic?
  - acute: develops over a period of < 48 hours
  - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
  - mild: 130-134 mmol/L
  - moderate: 120-129 mmol/L
  - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
  - patients with mild hyponatraemia may be symptomatic
  - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
  - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
  - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis

  - euvolemic hyponatraemia: SIADH
  - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients
- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected
- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
  - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
  - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider medications:
  - demeclocycline
  - vaptans (see below)

If a hypervolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):

- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia
- pathophysiology:
  - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
  - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

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Question 372 of 414 ✓

Which one of the following statements regarding glucagon-like peptide-1 (GLP-1) is **incorrect**?

Secreted in response to an oral glucose load	7%
[✓ Increased levels are seen in type 2 diabetes mellitus]	60%
Slows gastric emptying	13%
Secreted by the small intestine	10%
Responsible for the incretin effect	11%

Decreased levels of GLP-1 are seen in type 2 diabetes mellitus

👍 👎 Discuss (3) Improve

Next question

Diabetes mellitus: GLP-1 drugs

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
>
> - *BMI >= 35 kg/m² in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

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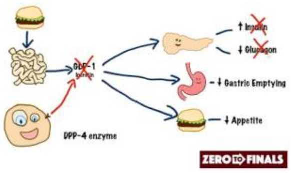
Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

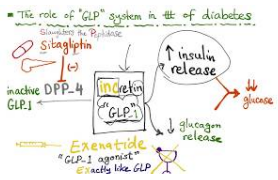
Report broken link

Media


↑ Insulin
↓ Glucagon
GLP-1
Incretin
− ↓ Gastric Emptying
— ↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

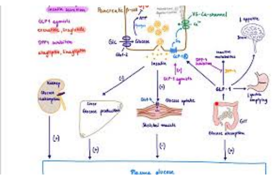
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2


The role of "GLP" system in ℞ of diabetes
Glucagon like Peptidase
Sitagliptin
(-)
inactive DPP-4
GLP-1
incretin
"GLP-1"
↑ insulin release
↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

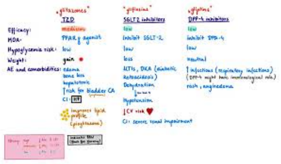
Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 26 👎 5



Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 23 👎 7

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Score: **23.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

PassMedicine

Question 373 of 414 ✗

A 76-year-old woman is brought in to the emergency department after carers noted she was drowsy in her residential home. She has had a 3 day history of severe diarrhoea and vomiting. On admission she has had multiple seizures which have responded to lorazepam.

Her vital signs are taken. Her respiratory rate is 12, heart rate is 89/min, blood pressure is 101/62mmHg, temperature is 37.2ºC. On examination she is making some snoring noises however is ventilating spontaneously. Her chest is clear. She has reduced skin turgor and a capillary refill time of 3 seconds. Her glasgow coma scale score is 11 and pupils are equal and reactive to light.

Blood tests are requested:

Hb	116 g/L	Male: (135-180) Female: (115 - 160)
Platelets	213 * 10^9/L	(150 - 400)
WBC	6.1 * 10^9/L	(4.0 - 11.0)
Na^+	109 mmol/L	(135 - 145)
K^+	5.2 mmol/L	(3.5 - 5.0)
Urea	6.7 mmol/L	(2.0 - 7.0)
Creatinine	118 µmol/L	(55 - 120)
CRP	13 mg/L	(< 5)

What is the most appropriate treatment for her hyponatraemia?

🟩	Bolus of hypertonic saline	42%
	Bolus of normal saline	8%
🟥	Infusion of loop diuretic	1%
	Infusion of hypertonic saline over 8 hours	41%
	Infusion of normal saline over 8 hours	9%

Hypertonic saline is usually indicated in patients with acute, severe, symptomatic hyponatraemia (< 120 mmol/L)

Important for me Less important

Severe hyponatraemia is treated with boluses of hypertonic saline until symptoms have resolved. As this woman is suffering from seizures and an ongoing reduction in consciousness with a sodium of <120mmol/L, a bolus of hypertonic saline is therefore indicated.

Normal saline does not have an adequate sodium content to correct this hyponatraemia and is therefore not used.

Loop diuretics may be used in mild hyponatraemia, particularly in the case of hypervolaemic hyponatraemia, however would not produce the immediate response required here.

Infusions of hypertonic saline over 8 hours may be useful in moderate hyponatraemia however due to the severity of the hyponatraemia here as well as the symptoms, this is not a sufficient rate in this case.

An infusion of normal saline over 8 hours would not be sufficient to correct the hyponatraemia.

👍 👎 💬 Discuss (5) Improve

Next question

Hyponatraemia: treatment ★

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:
- duration of hyponatremia: is it acute or chronic?
  - acute: develops over a period of < 48 hours
  - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
  - mild: 130-134 mmol/L

  - moderate: 120-129 mmol/L
  - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
  - patients with mild hyponatraemia may be symptomatic
  - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
  - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
  - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
  - euvolemic hyponatraemia: SIADH
  - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients
- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected
- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
  - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
  - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider medications:
  - demeclocycline
  - vaptans (see below)

If a hypervolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):
- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)
- can occur due to over-correction of severe hyponatremia
- pathophysiology:
  - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
  - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
  - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
  - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
  - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

Question 374 of 414 ✓

What causes increased sweating in patients with acromegaly?

Increased sodium content in sweat	3%
Raised basal metabolic rate	21%
Episodic hypoglycaemia	5%
Low-grade chronic pyrexia	1%
[✓ Sweat gland hypertrophy]	71%

Acromegaly: increased sweating is caused by sweat gland hypertrophy

Important for me Less important

Discuss (1) Improve

Next question

Acromegaly: features

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic.

Features

- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin: caused by sweat gland hypertrophy
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea
- 6% of patients have MEN-1

Complications

- hypertension
- diabetes (>10%)
- cardiomyopathy
- colorectal cancer

Next question

Textbooks

High-yield textbook

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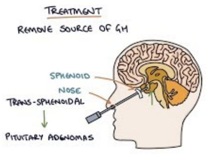
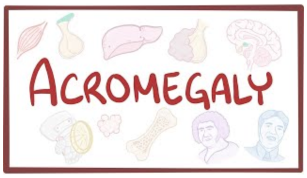
Media


TREATMENT
REMOVE SOURCE OF GH
SPHENOID
NOSE
TRANS-SPHENOIDAL
PITUITARY ADENOMAS

Understanding Acromegaly

Zero To Finals - YouTube 👍 24 👎 1


ACROMEGALY

Acromegaly

Osmosis - YouTube 👍 12 👎 1

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PassMedicine

Question 375 of 414 ✗

A 72-year-old woman presents with weight loss and a 6-month history of cough. Her blood tests show a raised serum calcium. You suspect a diagnosis of lung cancer.

What blood test result would support this diagnosis?

	Low parathyroid hormone related protein	15%
🟩	Low serum parathyroid hormone	67%
	Raised serum creatinine	1%
	Raised serum phosphate	10%
🟥	Raised serum vitamin D	6%

In hypercalcaemia secondary to malignancy, PTH is low, although PTHrP may be raised

Important for me Less important

A **low serum parathyroid hormone (PTH) level** would be indicative of an underlying malignancy. This is because in malignancy, hypercalcaemia is driven by bone metastases, PTHrP secretion from the tumour, or increased osteoclastic activity in myeloma, and therefore PTH would be suppressed.

Low parathyroid hormone-related protein is incorrect, as in certain malignancies PTHrP would be raised.

Raised serum creatinine could indicate other causes of hypercalcaemia such as milk-alkali syndrome, or chronic kidney disease.

Raised serum phosphate is not an indicator of an underlying malignancy.

High serum vitamin D level could indicate vitamin D toxicity rather than malignancy.

Discuss Improve

Next question

Hypercalcaemia: causes

Two conditions account for 90% of cases of hypercalcaemia:
- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
    - PTHrP from the tumour e.g. squamous cell lung cancer
    - bone metastases
    - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include
- sarcoidosis
    - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:
    - thiazides
    - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
    - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

Textbooks

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Extended textbook

Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€” presentation and management

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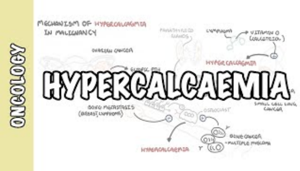
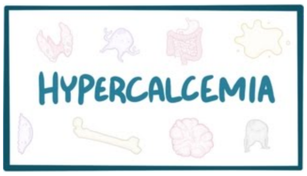
Media


ONCOLOGY
MECHANISM OF HYPERCALCAEMIA IN MALIGNANCY
HYPERCALCAEMIA
BONE METASTASIS (BREAST, LYMPHOMA)
SMALL CELL LUNG CANCER
BONE CANCER - MULTIPLE MYELOMA
HYPERCALCAEMIA

Hypercalcemia in malignancy

Armando Hasudungan - YouTube 👍 19 👎 2


HYPERCALCEMIA

Hypercalcemia

Osmosis - YouTube 👍 18 👎 7

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Score: **23.2%**

1 ✓

2 ✓

PassMedicine

Question 376 of 414 ✗

A 54-year-old woman who has had a hysterectomy presents for advice about hormone replacement therapy. Which one of the following would result from the use of a combined oestrogen-progestogen preparation compared to an oestrogen-only preparation?

	Decreased risk of venous thromboembolism	21%
	Increased risk of a stroke	13%
🟩	Increased risk of breast cancer	32%
🟥	Increased risk of endometrial cancer	22%
	Better control of symptoms	12%

HRT: adding a progestogen increases the risk of breast cancer

Important for me Less important

This is the rationale behind giving women who've had a hysterectomy oestrogen-only treatment. The BNF states that the stroke risk is the same regardless of whether the HRT preparation contains progesterone.

Discuss (11) Improve

Next question

Hormone replacement therapy: adverse effects

Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen (combined with a progestogen in women with a uterus) to help alleviate menopausal symptoms.

Side-effects

- nausea
- breast tenderness
- fluid retention and weight gain

Potential complications

- increased risk of breast cancer
  - increased by the addition of a progestogen
  - in the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
  - the increased risk relates to the duration of use
  - the risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT
- increased risk of endometrial cancer
  - oestrogen by itself should not be given as HRT to women with a womb
  - reduced by the addition of a progestogen but not eliminated completely
  - the BNF states that the additional risk is eliminated if a progestogen is given continuously
- increased risk of venous thromboembolism
  - increased by the addition of a progestogen
  - transdermal HRT does not appear to increase the risk of VTE
  - NICE state women requesting HRT who are at high risk for VTE should be referred to haematology before starting any treatment (even transdermal)
- increased risk of stroke
- increased risk of ischaemic heart disease if taken more than 10 years after menopause

Next question

Textbooks

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Links

NICE 👍 4 👎 0

2015 Menopause guidelines

The British Menopause Society and Women's Health Concern 👍 1 👎 2

Recommendations on hormone replacement therapy

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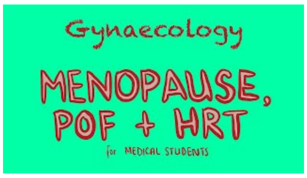
Media


Gynaecology
MENOPAUSE,
POF + HRT
for MEDICAL STUDENTS

Menopause

MedFlix - YouTube 👍 7 👎 2

Report broken media

Score: **23.1%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗
12 ✓
13 ✗
14 ✓
15 ✗

PassMedicine

Question 377 of 414

Which one of the following is least characteristic of Addison's disease?

Hypoglycaemia	9%
Metabolic alkalosis	59%
Hyponatraemia	4%
Hyperkalaemia	11%
Positive short ACTH test	17%

Addison's disease is associated with a metabolic acidosis

Important for me Less important

The correct answer is **Metabolic alkalosis**. Addison's disease, also known as primary adrenal insufficiency, is characterised by a deficiency in the hormones cortisol and aldosterone produced by the adrenal glands. This leads to symptoms such as hypoglycaemia, hyponatraemia, and hyperkalaemia. However, metabolic alkalosis is not a typical feature of Addison's disease.

Hypoglycaemia occurs in Addison's disease because cortisol plays a key role in maintaining blood glucose levels. Cortisol stimulates gluconeogenesis and glycogenolysis and antagonises insulin action. Therefore, its deficiency can lead to low blood sugar levels.

Hyponatraemia is another common feature of Addison's disease due to a deficiency of aldosterone which regulates sodium balance in the body. Aldosterone promotes the reabsorption of sodium (and water) in the kidneys while promoting potassium excretion. Thus, its deficiency results in sodium loss leading to hyponatraemia.

In contrast to hyponatraemia, **hyperkalaemia** occurs in Addison's disease due to a lack of aldosterone which normally promotes potassium excretion by the kidneys. Without adequate aldosterone, there is an accumulation of potassium in the body leading to hyperkalaemia.

The **short ACTH test**, also known as Synacthen or Cosyntropin test, is used for diagnosing adrenal insufficiency including Addison's disease. In this test, synthetic ACTH is given and then blood cortisol levels are measured before and after administration of synthetic ACTH. In normal individuals or those with secondary adrenal insufficiency (due to the pituitary gland), there will be an increase in cortisol levels post-ACTH administration. However, those with primary adrenal insufficiency like Addison's disease will have little or no increase in cortisol levels indicating that adrenals are unable to respond adequately making this test usually positive for people with Addison's disease.

👍 👎 Discuss (6) Improve

Next question

Addison's disease: investigations ★

In a patient with suspected Addison's disease the definite investigation is an ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If an ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:

- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 6 👎 4

2017 Adrenal insufficiency â€" recognition and management

Report broken link

Media

Primary adrenal insufficiency (Addison's disease)

Osmosis - YouTube 👍 22 👎 8

Addison's disease

Armando Hasudungan - YouTube 👍 12 👎 5

Report broken media

Score: **23.1%**

1 ✓
2 ✓
3 ✓
4 ✗

PassMedicine

Question 378 of 414 ✗

A 70-year-old male presents for advice regarding hyperlipidaemia. In the recent past he has trialled diet modification and exercise. He has a past history of hypertension and Type 2 diabetes, and his medications include aspirin, perindopril and metformin. He has a family history of his brother and mother having a coronary artery bypass grafting.

Total cholesterol	5	(Normal <5.2)
LDL cholesterol	2.5	(Normal <3.5)
HDL	1.1	(Normal >1)
Triglycerides	2.3	(Normal <1.5)

Which would be the most appropriate management choice to reduce his risk of cardiovascular events?

🟥	Cholestyramine	2%
🟩	Atorvastatin	64%
	Ezetimibe	12%
	Gemfibrozil	16%
	Omega 3 fatty acids	6%

The patient has an isolated hypertriglyceridaemia and significant cardiac risk factors. This is what the question is trying to demonstrate. While fibrates are well known to be effective against hypertriglyceridaemias, his risk factor burden is enough that a statin (which is also functional on triglyceride levels, not just LDLs) is the first choice in this situation. In particular, fibrates have not been shown to reduce cardiovascular events in the presence of diabetes, while statins have.

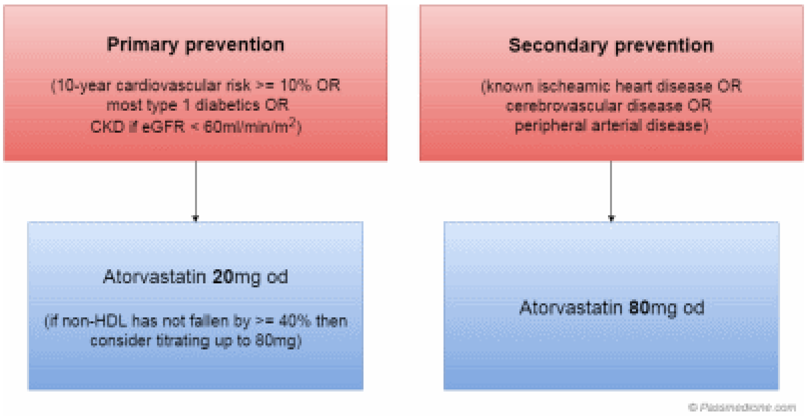
Thus, an isolated hypertriglyceridaemia in the presence of significant cardiovascular risk factors, in a patient not currently on a statin, should be managed with the introduction of a statin.

Discuss (8) Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months

- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet

- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity

- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation

- smokers should be encouraged to quit

Next question

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Links

NICE 👍 9 👎 6

2014 Lipid modification guidelines

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Question 379 of 414 ✗

Which one of the following statements regarding hypocalcaemia is **incorrect**?

	Most features are a result of neuromuscular excitability	13%
	Chronic hypocalcaemia may cause cataracts	35%
	Perioral paraesthesia is seen	3%
🟩	Chvostek's sign is more sensitive and specific than Trousseau's sign	40%
🟥	Prolonged QT interval is seen	9%

Hypocalcaemia: Trousseau's sign is more sensitive and specific than Chvostek's sign

Important for me Less important

The **incorrect** statement regarding hypocalcaemia is '**Chvostek's sign is more sensitive and specific than Trousseau's sign**'. In fact, Chvostek's sign, which involves twitching of the facial muscles in response to tapping over the area of the facial nerve, is less sensitive and specific for hypocalcaemia than Trousseau's sign. Trousseau's sign involves carpal spasm induced by inflating a blood pressure cuff above systolic pressure for 2-3 minutes; it has greater sensitivity and specificity for hypocalcaemia.

Discussing the other options:

'**Most features are a result of neuromuscular excitability**' is correct. Hypocalcaemia increases neuromuscular excitability because a decrease in extracellular calcium reduces the threshold potential of nerve cells, making them more likely to depolarise and transmit an action potential. This results in symptoms such as muscle cramps, tetany (involuntary contraction of muscles), paraesthesia (abnormal sensation like tingling or pricking), and seizures.

'**Chronic hypocalcaemia may cause cataracts**' is also correct. Chronic hypocalcaemia can lead to deposition of calcium in various tissues including the lens of the eye, resulting in cataract formation. However, this is a relatively rare complication compared to the more common neurological symptoms.

'**Perioral paraesthesia is seen**' is accurate as well. One common symptom of hypocalcaemia includes perioral paraesthesia (a feeling of numbness or tingling around the mouth). This occurs due to increased nerve excitability caused by low serum calcium levels.

Lastly, '**Prolonged QT interval is seen**' is true as well. Hypocalcaemia can affect cardiac function by prolonging the ST segment and QT interval on an ECG. This happens because low calcium levels slow down phase 2 (the plateau phase) of ventricular myocyte action potentials, thereby prolonging both ST segment and QT interval.

👍 👎 Discuss (6) Improve

Next question

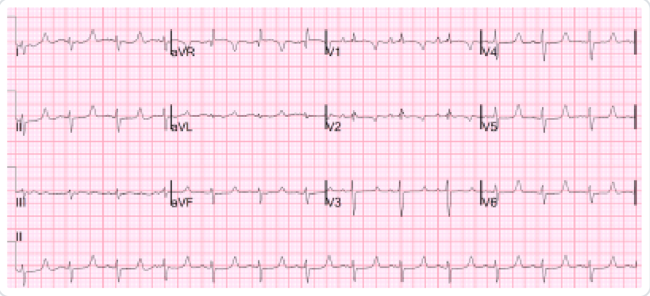
Hypocalcaemia: features ★

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features
- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Trousseau's sign
- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers are drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

Chvostek's sign
- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people


I
aVR
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V5
III
aVF
V3
V6
II

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HYPOCALCEMIA

Hypocalcemia

Osmosis - YouTube 👍 10 👎 2

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Score: **23%**

1 ✓

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Question 380 of 414 ✗

A 40-year-old woman presented with a several month history of increased sweating, anxiety, weight loss and heat intolerance.

On exam, she has anterior bulging of the eyes as well as difficultly moving the eyes in all directions. There are skin lesions present on the shins bilaterally, clubbing of the fingernails and swelling of both the hands and feet.

Blood tests show a low thyroid stimulation hormone (TSH) level, raised free T3 and T4, and the presence of TSH receptor stimulating antibodies.

What approximate percentage of patients with this diagnosis have these specific antibodies present?

	30%	10%
🟩	90%	61%
	25%	5%
🟥	75%	23%
	3%	1%

TSH antibodies are found in 90% of patients with Graves' disease and can help distinguish from other forms of hyperthyroidism

Important for me Less important

This patient has presented with the hallmark features of the autoimmune, thyrotoxicosis condition Grave's disease. Grave's disease is the commonest cause of thyrotoxicosis with patients presenting with symptoms of hyperthyroidism (e.g. sweating, tremor, weight loss, heat intolerance) normally along with specific Grave's features including ophthalmoplegia, exophthalmos, pretibial myxoedema and thyroid acropachy. Diagnosis is based on clinical features, thyroid function tests and the presence of TSH receptors stimulating antibodies which are found in approximately **90%** of cases.

Approximately **30%** of Grave's disease patients have eye signs which are not present in other forms of thyrotoxicosis. These eye signs include exophthalmos and ophthalmoplegia. A much higher percentage of cases have TSH receptor stimulating antibodies present.

Approximately **25%** of patients with hyperthyroidism experience hypercalcaemia secondary to stimulation of the osteoclasts resulting in increased calcium reabsorption and mobilisation from the bone.

Of patients with confirmed Grave's disease approximately **75%** have anti-thyroid peroxidase antibodies present on serum testing. A higher percentage of patients will have TSH receptors stimulating antibodies.

Grave's disease typically affects females more than males with approximately **3%** of all women developing the condition compared to 0.3% of men.

👍 👎 Discuss (2) Improve

Next question

Graves' disease: features

Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

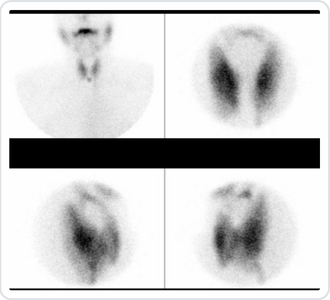
Features seen in Graves' but not in other causes of thyrotoxicosis
- eye signs (30% of patients)
  - exophthalmos
  - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
  - digital clubbing
  - soft tissue swelling of the hands and feet
  - periosteal new bone formation

Autoantibodies
- TSH receptor stimulating antibodies (90%)

- anti-thyroid peroxidase antibodies (75%)

Thyroid scintigraphy

- diffuse, homogenous, increased uptake of radioactive iodine



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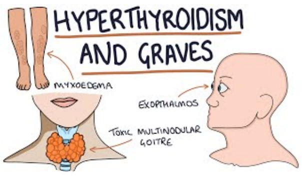
HYPERTHYROIDISM
AND GRAVES
MYXOEDEMA
EXOPTHALMOS
TOXIC MULTINODULAR GOITRE

[Understanding Hyperthyroidism and Graves' Disease]

Zero to Finals - YouTube 25 2

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← Question 381 of 414 ✗ →

A 31-year-old woman is diagnosed with familial hypercholesterolaemia. Genetic testing shows that she is heterozygous for the condition. You discuss the possibility of screening her relatives. What is the chance her brother will also be affected?

🟩 50%	73%
🟥 66%	2%
25%	18%
100%	4%
0%	2%

Familial hypercholesterolaemia is an autosomal dominant condition

Important for me Less important

As familial hypercholesterolaemia is an autosomal dominant condition 50% of the first-degree relatives of heterozygotes will be affected. Please see the PLoS link for more details.

Discuss (6) Improve

Next question

Familial hypercholesterolaemia ★

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Case finding:

- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
  - a total cholesterol level greater than 7.5 mmol/l and/or

  - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:
  - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
  - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome criteria**:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

Next question

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Links

The FH Foundation 👍 3 👎 1

Simon Broom Criteria

The FH Foundation 👍 3 👎 1

High cholesterol during preganancy

NICE 👍 3 👎 1

2008 Familial hypercholesterolaemia guidelines

Public Library of Science (PLoS) 👍 2 👎 1

Cascade Screening for Familial Hypercholesterolemia (FH)

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Media

FAMILIAL
HYPERCHOLESTEROLEMIA
OSMOSIS.org

Familial hypercholesterolaemia

Osmosis - YouTube 👍 20 👎 1

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Score: **22.8%**

1 ✓
2 ✓

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Question 382 of 414 ✗

A 50-year-old male, with known ischaemic heart disease and diabetes, is brought to the emergency department with a reduced GCS. He was recently started on a new anti-diabetic medication causing him to urinate more often. Previously, he was managed on insulin.

Examination reveals a middle-aged male lying unconscious on the bed with cold, clammy skin and fruity odour. His vitals are:

- BP 90/60 mmHg
- Heart rate 124/min
- Respiratory rate 28/min
- Temperature 36°C
- Urine output 1800 mL in last 24 hours
- Blood glucose 5 mmol/L

Labs show:

Hb	130 g/L	Male: (135-180) Female: (115 - 160)
Platelets	254 * 10^9/L	(150 - 400)
WBC	7.0 * 10^9/L	(4.0 - 11.0)

Cardiac enzymes are normal. Serum and urinary ketones are positive (3+).

What is the most likely diagnosis?

	Cardiogenic shock	1%
	Diabetic ketoacidosis	18%
🟥	Lactic acidosis	5%
🟩	Normoglycemic ketoacidosis	75%
	Septic shock	1%

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule

Important for me Less important

Patients who have diabetes mellitus and ischemic heart disease are usually started on SGLT-2 inhibitor drugs. These have shown to be beneficial in reducing the mortality associated with ischaemic heart disease. However, these drugs cause glycosuria leading to a number of side effects such as urogenital infection, Fournier gangrene, normoglycemic ketoacidosis and increased risk of lower-limb amputations.

In the above scenario, the patient with ischaemic heart disease was most probably started on an SGLT-2 inhibitor as evidenced by polyuria. The patient has a fruity odour caused by ketones and has a normal blood sugar level along with the vital signs which are indicative of shock. Thus, the patient is suffering from normoglycemic ketoacidosis.

The patient is not exhibiting any features of right or left-sided heart failure and his cardiac enzymes are normal therefore a diagnosis of cardiogenic shock is highly unlikely.

Diabetic ketoacidosis (DKA) is a common complication of diabetes that usually occurs among type I diabetic patients. It is associated with positive serum ketones and high blood sugar levels. This patients blood glucose was normal and therefore DKA is unlikely

Lactic acidosis is associated with metformin. This patient was probably started on a glycosuric drug as evidenced by the increased frequency of urination. Lactic acidosis can also be seen in shock-like states due to inadequate tissue perfusion. In this patient, urine output greater than 0.5mL/kg/hour indicates adequate tissue perfusion, making lactic acidosis an unlikely diagnosis.

Septic shock is unlikely as the patient has a normal white cell count without any signs and symptoms of an infective aetiology.

👍 👎 Discuss (2) Improve

Next question

SGLT-2 inhibitors ★

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include

- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

Next question

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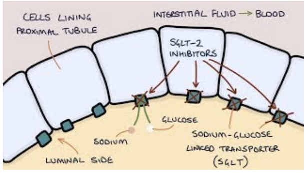
Links

BNF 👍 3 👎 9

Dapagliflozin

Report broken link

Media


CELLS LINING PROXIMAL TUBULE
INTERSTITIAL FLUID → BLOOD
SGLT-2 INHIBITORS
GLUCOSE
SODIUM
LUMINAL SIDE
SODIUM-GLUCOSE LINKED TRANSPORTER (SGLT)

How does Dapagliflozin work? Understanding SGLT2 inhibitors.

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Question 383 of 414 ✗

A 27-year-old man is reviewed in a fertility clinic. Semen analysis has revealed azoospermia. On examination at the previous appointment he was noted to be 1.83 metres tall with a body mass index of 25 kg / m^2. A degree of gynaecomastia is noted, testicular volume is around 10ml bilaterally and his visual fields were normal. Which investigation is likely to be diagnostic?

FISH analysis of DNA	5%
Prolactin level	9%
🟩 Karyotype	75%
MRI pituitary	9%
🟥 PCR analysis of DNA	3%

Klinefelter's? - do a karyotype

Important for me Less important

The correct answer in this case is **Karyotype**. A karyotype is a test that examines an individual's chromosomes to detect any abnormalities. In this scenario, the patient has azoospermia (absence of sperm in semen), gynaecomastia (enlarged breast tissue in males), and normal visual fields. These findings, along with his age and height, suggest the possibility of Klinefelter syndrome, which is a chromosomal disorder caused by the presence of an extra X chromosome (47, XXY). A karyotype would be diagnostic for this condition as it would reveal the additional X chromosome.

FISH analysis of DNA (fluorescence in situ hybridization) is a molecular cytogenetic technique used to detect specific DNA sequences on chromosomes. Although FISH can be helpful in identifying certain chromosomal abnormalities, it is not the most appropriate investigation for this patient as a karyotype would provide more comprehensive information about his overall chromosomal makeup.

Prolactin level would be relevant if the patient had symptoms suggestive of hyperprolactinaemia such as galactorrhoea or if there were signs of pituitary dysfunction like visual field defects. However, given that his visual fields are normal and gynaecomastia is more likely related to Klinefelter syndrome in this context, prolactin levels are less likely to be diagnostic.

An **MRI pituitary** would be indicated if there was suspicion of a pituitary tumour or other structural abnormality causing hormonal imbalances leading to infertility. However, since the patient's visual fields are normal and he has physical features consistent with Klinefelter syndrome, an MRI pituitary is less likely to yield a diagnosis in this case.

PCR analysis of DNA (polymerase chain reaction) is a molecular technique used to amplify specific DNA sequences. While PCR can be useful in diagnosing certain genetic disorders, it would not be the most appropriate test for this patient as Klinefelter syndrome is a chromosomal disorder that can be diagnosed using karyotyping.

👍 👎 Discuss (6) Improve

Next question

Klinefelter's syndrome

Klinefelter's syndrome is associated with karyotype 47, XXY.

Features
- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels but low testosterone

Diagnosis is by karyotype (chromosomal analysis).

Next question

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Question 384 of 414 ✗

A 54-year-old patient presents to his general practitioner for a review of his diabetes treatment. He takes metformin. He is worried about adding additional medications that might cause hypoglycaemia. He has a past medical history of bladder cancer, which was surgically treated.

The examination is unremarkable other than an elevated body mass index (32 kg/m^2).

Recent blood test results:

HbA1c	61 mmol/L	(<48)

His GP would like to commence him on a medication that does not cause weight gain or hypoglycaemia.

What is the likely mechanism of action of this drug?

Agonist of PPAR-gamma receptor	9%
Binding of ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells	8%
Exogenous insulin	1%
Inhibition of intestinal alpha glucosidases	5%
Reduction of the peripheral breakdown of incretins such as glucagon-like peptide (GLP-1)	76%

Gliptins (DPP-4 inhibitors) reduce the peripheral breakdown of incretins such as GLP-1

Important for me Less important

Reduction of the peripheral breakdown of incretins such as GLP-1 is the correct answer. This is the mechanism of action of the gliptin class of medication (DPP-4 inhibitors). They are an option for add on treatment of type 2 diabetes if blood glucose is not controlled by metformin. They are not typically associated with weight gain or hypoglycaemia.

Binding of ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells is incorrect. This is the mechanism of action of sulphonylureas, which cause both weight gain and hypoglycaemia.

Exogenous insulin is incorrect. This causes weight gain and hypoglycaemia.

Inhibition of intestinal alpha glucosidases is incorrect. This is the mechanism of action of acarbose. While this does not cause weight gain or hypoglycaemia, it does not feature in current NICE guidance as a recommended option for add on treatment for type 2 diabetes if metformin is insufficient or not tolerated.

Agonist of the PPAR-gamma receptor is incorrect. This is the mechanism of action of thiazolidinediones. This class of medication is associated with weight gain. Furthermore, it is contraindicated in those patient with current or previous bladder cancer.

👍 👎 Discuss (4) Improve

Next question

Diabetes mellitus: GLP-1 drugs ★

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in

T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m^2 in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m^2 and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

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Links

NICE 👍 12 👎 7

2022 Type 2 diabetes guidelines

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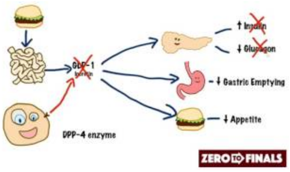
Media


↑ Insulin
↓ Glucagon
GLP-1
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

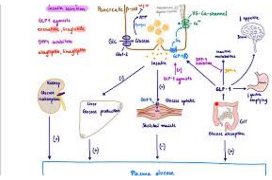
How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 👍 45 👎 2

The role of "GLP" system in ℞ of diabetes
Sitagliptin
inactive GLP-1
DPP-4
incretin
"GLP"
↑ insulin release
↓↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

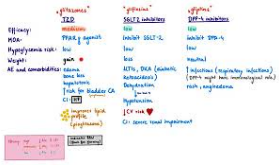
Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 👍 41 👎 7



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 26 👎 5



Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 23 👎 7

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Score: **22.7%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗
9 ✓
10 ✗
11 ✗

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Question 385 of 414 ✕

A 50-year-old man is being treated for community-acquired pneumonia on a general medical ward. His past medical history includes type 2 diabetes mellitus, for which he takes metformin and insulin. The nurses report that today the patient appears sweaty, shaky and mildly confused. A capillary blood glucose is taken and shows a reading of 2.9mmol/L.

The secretion of what hormone is increased first in response to this condition?

Adrenaline	8%
Cortisol	14%
🟩 Glucagon	72%
🟥 Growth hormone	3%
Insulin	4%

Glucagon is the first hormone secreted in response to hypoglycaemia

Important for me Less important

This patient is symptomatic of hypoglycaemia, whereby his blood glucose has fallen below 4.0mmol/L. Common symptoms of hypoglycaemia include sweating, shaking, nausea, anxiety, weakness, confusion, and altered vision. In rare cases, severe hypoglycaemia can cause reduced consciousness, coma or convulsions. Hypoglycaemia in this patient is the result of insulin treatment during acute illness. Blood glucose levels are often erratic during acute illness, and insulin doses may require significant adjustments.

The first hormone secreted in response to hypoglycaemia is **glucagon**. Following glucagon secretion, there is also increased catecholamine-mediated (**adrenergic**) and acetylcholine-mediated (cholinergic) neurotransmission. These responses trigger the autonomic symptoms of hypoglycaemia, such as sweating, shaking, nausea and anxiety.

Cortisol and **growth hormone** are also secreted in response to hypoglycaemia, but this occurs after glucagon secretion.

Insulin secretion is decreased in response to hypoglycaemia rather than increased. This decrease in secretion is the first response, followed by glucagon secretion.

👍 👎 Discuss Improve

Next question

Hypoglycaemia ★

Causes

- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol
  - causes exaggerated insulin secretion
  - mechanism is thought to be due to the effect of alcohol on the pancreatic microcirculation → redistribution of pancreatic blood flow from the exocrine into the endocrine parts → increased insulin secretion
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia

- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

Features

- blood glucose levels and the severity of symptoms are not always correlated, especially in patients with diabetes.
- blood glucose concentrations <3.3 mmol/L cause autonomic symptoms due to the release of glucagon and adrenaline (average frequency in brackets):
  - Sweating
  - Shaking
  - Hunger
  - Anxiety
  - Nausea

- blood glucose concentrations below <2.8 mmol/L cause neuroglycopenic symptoms due to inadequate glucose supply to the brain:
    - Weakness
    - Vision changes
    - Confusion
    - Dizziness
- Severe and uncommon features of hypoglycaemia include:
    - Convulsion
    - Coma

Management of hypoglycaemia

- the following guidelines are based on the BNF hypoglycaemia treatment summary.
- in the community (for example, diabetes mellitus patients who inject insulin):
    - Initially, oral glucose 10-20g should be given in liquid, gel or tablet form
    - Alternatively, a propriety quick-acting carbohydrate may be given: GlucoGel or Dextrogel.
    - A 'HypoKit' may be prescribed which contains a syringe and vial of glucagon for IM or SC injection at home
- in a hospital setting:
    - If the patient is alert, a quick-acting carbohydrate may be given (as above)
    - If the patient is unconscious or unable to swallow, subcutaneous or intramuscular injection glucagon may be given.
    - Alternatively, intravenous 20% glucose solution may be given through a large vein

Next question

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Postgraduate Medical Journal

PassMedicine

Question 386 of 414 ✓

A 36-year-old woman who is currently 32 weeks pregnant has been monitoring her capillary blood glucose (CBG) at home following a diagnosis of gestational diabetes mellitus (GDM) 4 weeks ago.

She has been given appropriate dietary and exercise advice, as well as review by a dietitian. She has also been taking metformin and has been on the maximum dose for the past 2 weeks.

Fetal growth scans have been normal with no signs of macrosomia or polyhydramnios.

She has brought her CBG diary today, which shows that her mean pre-meal CBG is 5.9 mmol/L and mean 1-hour postprandial CBG is 8.3 mmol/L.

What is the most appropriate management?

Add gliclazide	1%
Add sitagliptin	1%
[✓ Commence insulin]	77%
Stop metformin	1%
Continue current treatment and review in 2-3 weeks	19%

In gestational diabetes, if blood glucose targets are not met with diet/metformin then insulin should be added

Important for me Less important

Pregnant women with GDM should be advised to maintain their CBGs below the following target levels:

- fasting: 5.3mmol/L

AND

- 1 hour postprandial: 7.8 mmol/L or
- 2 hours postprandial: 6.4 mmol/L

If these targets are not met with diet, exercise and metformin, then insulin should be offered as add-on therapy.

The only sulphonylurea that is advocated by the National Institute of Health and Clinical Excellence (NICE) is glibenclamide, which can be considered in women who decline insulin, or who cannot tolerate metformin initially, hence gliclazide is an incorrect option here. Note that the use of any sulphonylurea in GDM is an off-license indication.

There is insufficient evidence to advise the safe use of gliptins in pregnancy, hence it is currently not recommended in GDM management.

It would not be correct to continue the same management or de-escalate treatment by stopping metformin as the CBG readings are above target levels. Although fetal growth is currently normal, there are serious ongoing risks to both mother and fetus if glycaemic control is not achieved, including pre-eclampsia, pre-term labour, stillbirth and neonatal hypoglycaemia.

👍 👎 Discuss (3) Improve

Next question

Gestational diabetes ★

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:
- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes
- BMI of > 30 kg/m^2
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

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Extended textbook

Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

NICE 👍 3 👎 5

2015 Management of diabetes in pregnancy

Report broken link

Media

PassMedicine

← Question 387 of 414 ✗ →

A 26-year-old student presents with increased thirst. As a result, he is waking up frequently at night to pass urine and not resting adequately. He is very worried that this may be diabetes due to his family history.

His most recent blood tests showed the following:

HbA1c	40 mmol/mol (< 48)

You suspect the underlying cause may be psychogenic polydipsia and request urine and serum osmolality to confirm.

What are these tests most likely to show if your suspicion is correct?

	A very high baseline serum osmolality	2%
🟩	High urine osmolality after fluid deprivation and high urine osmolality after desmopressin	69%
	High urine osmolality after fluid deprivation and low urine osmolality after desmopressin	12%
🟥	Low urine osmolality after fluid deprivation and high urine osmolality after desmopressin	8%
	Low urine osmolality after fluid deprivation and low urine osmolality after desmopressin	9%

Water deprivation test: primary polydipsia
- urine osmolality after fluid deprivation: high
- urine osmolality after desmopressin: high

Important for me Less important

High urine osmolality after fluid deprivation and after desmopressin is the correct answer as this is the normal response to these tests: the urine should concentrate (i.e. the osmolality should increase). If the polydipsia is of psychogenic nature, the kidneys can generally concentrate the urine normally (although this can be temporarily altered by drinking excessive amounts of water), so the osmolality will be high both in response to dehydration and to desmopressin, a synthetic version of antidiuretic hormone (ADH).

> In diabetes insipidus, the serum is very concentrated (high osmolality) and the urine is very dilute (low osmolality). If the source is central/cranial (lack of ADH production), this can be corrected with desmopressin which will cause the urine to concentrate (higher urine osmolality). If the source is nephrogenic (the kidneys do not respond to ADH), the urine remains dilute (low osmolality) even after desmopressin.

Low urine osmolality after fluid deprivation and high urine osmolality after desmopressin would suggest that the kidneys do respond to ADH by concentrating urine, however, ADH is not being produced by the hypothalamus, therefore pointing to cranial diabetes insipidus. In this case, we are suspecting psychogenic polydipsia which would not cause these results.

Low urine osmolality after fluid deprivation and low urine osmolality after desmopressin would suggest that the kidneys do not respond to ADH and point to nephrogenic diabetes insipidus, which is not the diagnosis we are suspecting here.

High urine osmolality after fluid deprivation and low urine osmolality after desmopressin is incorrect. You would not expect a low urine osmolality (dilute urine) after giving desmopressin unless, again, the kidneys were not responding to ADH correctly, meaning the patient had nephrogenic diabetes insipidus, in which case the urine osmolality would also be low after deprivation.

A very high baseline serum osmolality would be found in diabetes insipidus (the water deprivation test would then be needed to determine whether the cause is cranial or nephrogenic). The baseline serum osmolality will be low in psychogenic polydipsia as the serum will be dilute due to drinking excessive amounts of water.

👍 👎 Discuss Improve

Next question

Water deprivation test

The water deprivation test is designed to help evaluate patients who have polydipsia.

Method
- prevent patient drinking water
- ask the patient to empty their bladder

- hourly urine and plasma osmolalities

	Starting plasma osm.	Final urine osm.	Urine osm. post-DDAVP
Normal	Normal	> 600	> 600
Psychogenic polydipsia	Low	> 400	> 400
Cranial DI	High	< 300	> 600
Nephrogenic DI	High	< 300	< 300

Next question

Textbooks

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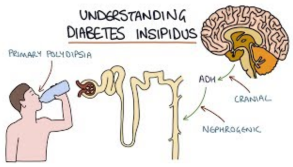
Media


UNDERSTANDING DIABETES INSIPIDUS
PRIMARY POLYDIPSIA
ADH
CRANIAL
NEPHROGENIC

Understanding Diabetes Insipidus

Zero to Finals - YouTube 👍 76 👎 5

PassMedicine

← Question 388 of 414 ✗ ⚐ →

A 49-year-old female was admitted to the emergency department with confusion. A history is unobtainable due to this confusion, with a Glasgow coma scale score of 13/15. Hospital records note a 2-month background of recurrent urinary tract infections (UTI's) and recent admission for urosepsis. Her past medical history includes: Type 2 diabetes mellitus, hypertension, hypercholesterolaemia and a hiatus hernia.

On examination the patient is cool peripherally with a cap refill of 3 seconds, dry mucus membranes, heart sounds 1+2+0, vesicular breath sounds, abdomen was soft, but tender over the suprapubic area. There was no rigidity or guarding and bowel sounds were present.

Observations: Respiratory rate 16 breaths per minute, saturations 98% on air, blood pressure 80/58mmHg, heart rate 122 beats per minute, temperature 38.4ºC and capillary glucose 16 mmol/L.

Urine dip showed:

Nitrites	+++
Leucocyte esterase	+++
Blood	+
Glucose	+++
Ketones	-
Protein	-

Which medication is likely to contributing to the cause of her presentations?

🟥	Metformin	5%
	Tolbutamide	3%
🟩	Dapaglifozin	84%
	Sitagliptin	6%
	Exanetide	2%

Dapagliflozin is a member of the glofozin anti-diabetic drugs. The medication works by inhibiting the sodium-glucose transport proteins (SGLT2), which reabsorbs glucose in the proximal tubule. The drug has recently been licensed by national institute of clinical excellence (NICE) for the treatment of type 2 diabetes mellitus. Dapagliflozin can be tried if blood sugars are poorly controlled following commencement of metformin and the patient is unable to take a sulfonylurea. Common side effects are often secondary to the glycosuria, which include increased predisposition of urinary tract infection and dehydration.

Discuss (6) Improve

Next question

Diabetes mellitus: GLP-1 drugs

A number of drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)

Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

> *Consider adding exenatide to metformin and a sulfonylurea if:*
> - *BMI >= 35 kg/m² in people of European descent and there are problems associated with high weight, or*
> - *BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a > 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)

Key points

- dipeptidyl peptidase-4, DPP-4 inhibitors increase levels of incretins (GLP-1 and GIP) by decreasing their peripheral breakdown
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

Next question

Textbooks

High-yield textbook

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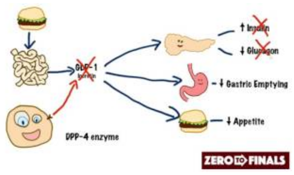
Links

NICE 12 7

2022 Type 2 diabetes guidelines

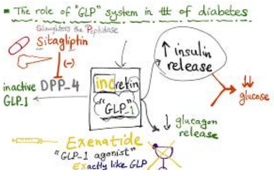
Report broken link

Media


GLP-1
↑ Insulin
↓ Glucagon
↓ Gastric Emptying
↓ Appetite
DPP-4 enzyme
ZERO TO FINALS

How does sitagliptin work? DPP-4 inhibitors and GLP-1 mimetics

Zero to Finals - YouTube 45 2


The role of "GLP" system in tt of diabetes
Sitagliptin
(-)
inactive DPP_4
GLP.1
incretin
"GLP-1"
↑ insulin release
↓ glucose
↓ glucagon release
Exenatide
"GLP-1 agonist"
Exactly like GLP

Glucagon-like Peptide (GLP-1) and the treatment of diabetes

Medicosis Perfectionalis - YouTube 41 7

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← Question 389 of 414 ✗ ⚐ →

You are called to see a patient overnight who had a total parathyroidectomy earlier in the day for primary hyperparathyroidism. The patient is experiencing perioral tingling and leg cramps. The nurse tells you that his hand clenched into a claw when she took his blood pressure. You suspect an electrolyte imbalance. Which ECG finding are you most likely to see with this electrolyte disorder?

	Tented T waves	2%
	Flattening of the P wave	3%
🟩	Prolongation of the QTc interval	84%
🟥	Prolongation of the QRS interval	7%
	Torsades de pointes	4%

The most common ECG change in hypocalcaemia is prolongation of the QTc interval

Important for me Less important

The correct answer is a prolongation of the QTc interval. The patient has the classic symptoms of acute hypocalcaemia. This is common after parathyroidectomy for primary hyperparathyroidism, due to rapid absorption of calcium into the bones after removal of excess PTH (often called 'hungry bones syndrome.') QTc prolongation in hypocalcaemia is mainly due to prolongation of the ST segment as a result of the slowing of ventricular repolarisation.

Torsades de pointes can be seen in hypocalcaemia but it is more commonly seen with hypokalaemia or hypomagnesaemia. Tented T waves and flattening of the P wave are seen in hyperkalaemia.

ECG diagnosis: the effect of ionised serum calcium levels on electrocardiogram
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3951043/

👍 👎 Discuss Improve

Next question

Hypocalcaemia: features

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features

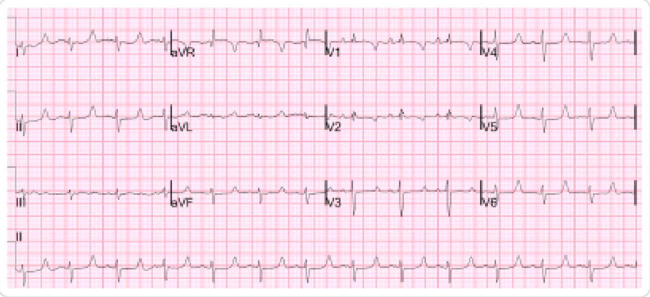
- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Trousseau's sign

- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers are drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people



Next question

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Question 390 of 414 ✓

A 52-year-old man was admitted with an altered mental status, paraesthesia and severe hypertension. For the last 3-months, he was suffering from fatigue, intermittent paraesthesia of all limbs, polyuria, weight gain, and irritability. The patient worked as an accountant with a 15 pack-year smoking history and would occasionally drink alcohol. He lived a sedentary life, and was obese from childhood, being unable to lose weight through his diet.

A venous blood gas was performed on admission:

pH	7.55	(7.35-7.45)
Na+	145 mmol/L	(133-146)
K+	3 mmol/L	(3.5-5.5)
HCO3-	40 mmol/L	(22-26)

What is the most likely diagnosis in this case?

Addison's disease	10%
Cushing's syndrome	70%
Nelson's syndrome	13%
Pheochromocytoma	6%
Pyloric stenosis	1%

Cushing's syndrome - hypokalaemic metabolic alkalosis

Important for me Less important

Hypokalaemia and metabolic alkalosis are more common in Cushing's syndrome caused by ectopic adrenocorticotropic hormone (ACTH) production (90%) than in other causes of Cushing's syndrome due to the enhanced mineralocorticoid effect. Given this patient's significant smoking history, a diagnosis of small-cell lung cancer with ectopic ACTH syndrome.

Pyloric stenosis classically gives an electrolyte and acid-base imbalance of hypochloraemic, hypokalaemic metabolic alkalosis but the absence of symptoms of pyloric stenosis such as vomiting, weight loss and altered bowel habits makes this diagnosis unlikely in this case.

Nelson's syndrome is a rare clinical manifestation that occurs as a complication of bilateral adrenalectomy, which is a procedure used to control hypercortisolism in patients with Cushing's disease. It is associated with a clinical triad of hyperpigmentation, excessive adrenocorticotropin secretion, and a corticotroph adenoma. The absence of adrenalectomy and associated clinical features makes the diagnosis unlikely.

Addison's disease is incorrect as it typically causes metabolic acidosis with hyponatraemia and hyperkalaemia during a crisis. Patients would typically have unexplained fever, weight loss, vomiting, and diarrhoea with abdominal pain, which is absent.

Pheochromocytoma is not correct as this tumour of the adrenal medulla would result in severe hypertension, headache, palpitations, and sweating.

Discuss (5) Improve

Next question

Cushing's syndrome: investigations ★

This section will consider:
- the general lab findings consistent with Cushing's syndrome
- tests to confirm whether a patient indeed has Cushing's syndrome
- tests to find the underlying cause of Cushing's syndrome

It is useful to bear in mind the possible causes:
- iatrogenic: corticosteroid therapy
- ACTH-dependent causes
  - Cushing's disease (a pituitary adenoma → ACTH secretion)
  - ectopic ACTH secretion secondary to a malignancy
- ACTH-independent causes
  - adrenal adenoma

General findings consistent with Cushing's syndrome

A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance.

Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels.

Tests to confirm Cushing's syndrome

The three most commonly used tests are:

- overnight (low-dose) dexamethasone suppression test
    - this is the most sensitive test and is now used first-line to test for Cushing's syndrome
    - patients with Cushing's syndrome do not have their morning cortisol spike suppressed
- 24 hr urinary free cortisol
    - two measurements are required
- bedtime salivary cortisol
    - two measurements are required

Localisation tests

The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

High-dose dexamethasone suppression test

The high-dose dexamethasone suppression test may be used to localise the pathology resulting in Cushing's syndrome. This test may be interpreted as follows:

Cortisol	ACTH	Interpretation
Not suppressed	Suppressed	Cushing's syndrome due to other causes (e.g. adrenal adenomas)
Suppressed	Suppressed	Cushing's disease (i.e. pituitary adenoma → ACTH secretion)
Not suppressed	Not suppressed	Ectopic ACTH syndrome

Other tests

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic

ACTH secretion.

An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's.

Next question

Textbooks

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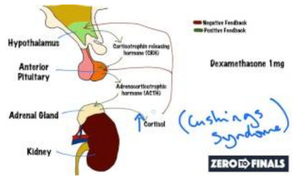
Media

CUSHING SYNDROME

Cushing syndrome

Osmosis - YouTube 👍 35 👎 2


Negative Feedback
Positive Feedback
Hypothalamus
Corticotrophin releasing hormone (CRH)
Anterior Pituitary
Dexamethasone 1mg
Adrenocorticotrophic hormone (ACTH)
Adrenal Gland
Cortisol
(Cushing's Syndrome)
Kidney
ZERO TO FINALS

Understanding The Dexamethasone Suppression Test

Zero to Finals - YouTube 👍 118 👎 8

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Question 391 of 414 ✓

Which one of the following types of oral steroid has the least amount of mineralocorticoid activity?

Fludrocortisone	12%
Hydrocortisone	11%
Dexamethasone	50%
Prednisolone	20%
Cortisone	7%

This is clinically relevant as there are some situations where it is important to combine high glucocorticoid (anti-inflammatory) activity with minimal mineralocorticoid (fluid-retention) effects. A good example is the use of dexamethsone for patients with raised intracranial pressure secondary to brain tumours.

Discuss (8) Improve

Next question

Corticosteroids

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity,	**Glucocorticoid activity, high mineralocorticoid activity,**	**Predominant glucocorticoid activity, low mineralocorticoid activity**	**Very high glucocorticoid activity, minimal mineralocorticoid activity**
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

The side effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects
- endocrine
  - impaired glucose regulation
  - increased appetite/weight gain
  - hirsutism
  - hyperlipidaemia
- Cushing's syndrome
  - moon face
  - buffalo hump
  - striae
- musculoskeletal
  - osteoporosis
  - proximal myopathy
  - avascular necrosis of the femoral head
- immunosuppression
  - increased susceptibility to severe infection
  - reactivation of tuberculosis
- psychiatric
  - insomnia
  - mania
  - depression
  - psychosis
- gastrointestinal
  - peptic ulceration
  - acute pancreatitis
- ophthalmic
  - glaucoma
  - cataracts

- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
- longer-term systemic corticosteroids suppress the natural production of endogenous steroids. They should therefore not be withdrawn abruptly, as this may precipitate an Addisonian crisis
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have:
    - received more than 40mg prednisolone daily for more than one week
    - received more than 3 weeks of treatment
    - recently received repeated courses

Next question

Textbooks

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Score: **23%**

1 ✓
2 ✓

Question 392 of 414 ✗

Each one of the following is associated with hyperkalaemia, except:

	Rhabdomyolysis	4%
🟩	Carbenoxolone	54%
	Acute renal failure	4%
🟥	Ciclosporin	16%
	Addison's	21%

The correct answer is **Carbenoxolone**. Carbenoxolone is a synthetic derivative of glycyrrhizinic acid, which is used for the treatment of peptic ulcer. It has mineralocorticoid activity and can cause hypokalaemia (low potassium levels), not hyperkalaemia (high potassium levels).

Discussing the incorrect options:

Rhabdomyolysis is associated with hyperkalaemia. This condition involves the breakdown of muscle tissue, leading to the release of intracellular contents, including potassium, into the bloodstream. This can result in an increased level of potassium in the blood.

Acute renal failure, also known as acute kidney injury, can be associated with hyperkalaemia. The kidneys play a crucial role in maintaining electrolyte balance, including potassium. When they fail to function properly, they may not excrete enough potassium, leading to its accumulation in the body.

Ciclosporin, an immunosuppressant medication often used after organ transplants to prevent rejection, can cause hyperkalaemia as one of its side effects. It impairs renal function and interferes with normal potassium excretion.

Finally, **Addison's disease**, or primary adrenal insufficiency, leads to decreased production of aldosterone by the adrenal glands. Aldosterone plays a key role in regulating sodium and potassium balance. Its deficiency results in sodium loss and retention of potassium by the kidneys, thus causing hyperkalaemia.

Discuss (4) Improve

Next question

Hyperkalaemia

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia:

- acute kidney injury
- drugs*: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, ciclosporin, heparin**
- metabolic acidosis
- Addison's disease
- rhabdomyolysis
- massive blood transfusion

Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

Next question

PassMedicine

Question 393 of 414 ✗

A 73-year-old woman presents with a two-month history of hoarse voice and dysphasia. She is otherwise well with no night sweats or weight loss. She has a history of hypertension, hypercholesterolaemia, and Hashimoto's thyroiditis.

On examination, there is an enlarged right-sided thyroid gland.

Fine needle aspiration demonstrates lymphocytic thyroiditis. She subsequently undergoes a right hemithyroidectomy. The histologic examination demonstrates extranodal marginal B-cells.

What is the most likely underlying diagnosis?

	Anaplastic thyroid cancer	12%
🟥	Hodgkin's lymphoma	18%
🟩	MALT lymphoma	54%
	Medullary thyroid cancer	10%
	Papillary thyroid cancer	6%

Hashimoto's thyroiditis is associated with the development of MALT lymphoma

Important for me Less important

Mucosa-associated lymphoid tissue (MALT) lymphoma is correct. Although this is a rare form of thyroid lymphoma it is associated with a previous history of Hashimoto's thyroiditis and histology shows extranodal marginal B-cells.

Anaplastic thyroid cancer is rare (1-2% of thyroid cancers). It tends to occur in older and he histology shows spindle and giant cells.

Hodgkin's lymphoma tends to present with more generalised lymphadenopathy, fatigue, weight loss, and night sweats.

Medullary thyroid cancer originates from the parafollicular cells (C cells), which produce the hormone calcitonin. The associated hormone secretion can cause diarrhoea symptoms. This cancer is often associated with multiple endocrine neoplasia syndromes (MEN) rather than Hashimoto thyroiditis.

Although papillary carcinoma is the most common type of thyroid cancer (80% of thyroid cancer cases), it tends to be slow-growing and affects younger patients. They are not associated with a history of Hashimoto's thyroiditis.

Discuss (4) Improve

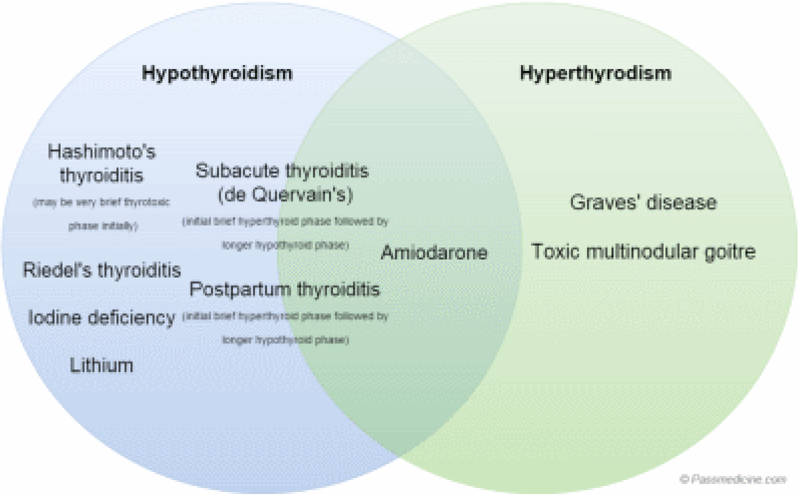
Next question

Hashimoto's thyroiditis ★

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features
- features of hypothyroidism
- goitre: firm, non-tender
- anti-thyroid peroxidase (TPO) and also anti-thyroglobulin (Tg) antibodies

Associations
- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of MALT lymphoma


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Riedel's thyroiditis
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Iodine deficiency
Lithium
Graves' disease
Toxic multinodular goitre
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Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of

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Question 394 of 414 ✗

An 82-year-old male nursing home resident with advanced vascular dementia presents with worsening confusion to the Emergency Department. His only regular medication is clopidogrel. His admission blood tests are as follows:

Na+	121 mmol/l
K+	3.8 mmol/l
Urea	9.4 mmol/l
Creatinine	110 umol/l

His confusion screen (including CT brain) is normal. On examination he has dry mucous membranes, his blood pressure is 104/58 mmHg, pulse 94/min and temperature 36.1°C. With regard to his low sodium what would be the most appropriate management?

	Fluid restriction	15%
	Demeclocycline	4%
🟩	Intravenous normal saline	76%
🟥	Tolvaptan	4%
	Furosemide	1%

This case is an example of hypovolaemic hyponatraemia. It is important with hyponatraemia to ascertain volume status as this will determine management. Poor oral intake due to advancing dementia is the likely cause. This is supported by an elevated urea suggesting dehydration. Poor oral intake can lead to both hyper or hyponatraemia depending on the relative proportions of sodium and water deficiency.

The management of each is as follows:

Hypovolaemic hyponatraemia
- rehydration with sodium chloride 0.9% or a balanced crystalloid (Hartmann's)
- avoid rapid correction of sodium in order to reduce the risk of osmotic complications such as central pontine myelinolysis

Euvolaemic hyponatraemia
- check urine and serum osmolality. Does the patient meet the criteria for SIADH?
- treat the underlying cause where possible in SIADH
- fluid restriction (500-750mls/day)
- monitor fluid balance and perform daily weights
- consider demeclocycline or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone.

Hypervolaemic hyponatraemia
- fluid and salt restriction
- consider diuretics
- treat the underlying cause (e.g. cardiac failure)

Discuss (4) Improve

Next question

Hyponatraemia: treatment ★

Untreated, severe hyponatraemia may result in cerebral oedema, which in turn can cause brain herniation. It is therefore important to promptly identify and treat hyponatremia appropriately. However, the particular management for each patient is based on a number of factors listed below. Further to this, over-rapid correction may result in osmotic demyelination syndrome.

Principles

Management of hyponatremia is complicated and primarily based on the following parameters:
- duration of hyponatremia: is it acute or chronic?
    - acute: develops over a period of < 48 hours
    - chronic: develops over a period > 48 hours
- the severity of hyponatremia: what is the sodium level?
    - mild: 130-134 mmol/L
    - moderate: 120-129 mmol/L
    - severe: < 120 mmol/L
- symptoms: is the patient symptomatic?
    - patients with mild hyponatraemia may be symptomatic

    - early symptoms may include: headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps
    - late symptoms may include: seizures, coma, and respiratory arrest
- the suspected aetiology of the hyponatraemia:
    - hypovolemic hyponatraemia/clinically dehydrated: diuretic stage of renal failure, diuretics, Addisonian crisis
    - euvolemic hyponatraemia: SIADH
    - hypervolaemic hyponatraemia: heart failure, liver failure, nephrotic syndrome

Management

Initial steps in all patients
- exclude a spurious result (e.g. blood taken from a drip arm)
- review medications that may cause hyponatraemia

Chronic hyponatreamia without severe symptoms

If a hypovolemic cause is suspected
- normal, i.e. isotonic, saline (0.9% NaCl)
- this may sometimes be given as a trial
    - if the serum sodium rises this supports a diagnosis of hypovolemic hyponatraemia
    - if the serum sodium falls an alternative diagnosis such as SIADH is likely

If a euvolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider medications:
    - demeclocycline
    - vaptans (see below)

If a hypervolemic cause is suspected
- fluid restrict to 500-1000 mL/day
- consider loop diuretics
- consider vaptans

Acute hyponatreamia with severe symptoms

Patients with acute, severe (<120 mmol/L) or symptomatic hyponatraemia require close monitoring, preferably in an HDU or above setting.

Hypertonic saline (typically 3% NaCl) is used to correct the sodium level more quickly than would be done in patients with chronic hyponatraemia.

Notes on specific medications

Vasopressin/ADH receptor antagonists (vaptans):

- these act primarily on V2 receptors - antagonism of V2 receptors results in selective water diuresis, sparing the electrolytes
- They should be avoided in patients who have hypovolemic hyponatremia
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications of treatment

Osmotic demyelination syndrome (central pontine myelinolysis)

- can occur due to over-correction of severe hyponatremia
- pathophysiology:
    - thought to develop secondary to astrocyte (and possibly oligodendrocyte) apoptosis
    - astrocytes and oligodendrocytes (cells of the glial syncytium) are crucial for normal myelination
    - chronic hyponatraemia → loss of osmotically active organic osmolytes (such as myoinositol, glutamate, glutamine) from astrocytes. These provide protection against cerebral oedema
    - organic osmolytes cannot be replaced quickly enough when the brain volume begins to shrink in response to the correction of hyponatraemia
    - the dehydrated astrocytes and oligodendrocytes undergo apoptosis or other forms of injury → demyelination
- to avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period
- symptoms usually occur after 2 days and are usually irreversible: dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma
- patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

Next question

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← Question 395 of 414 ✗ ⚐ →

A 31-year-old female is under investigation for Addison's disease after presenting with feeling tired all the time, weight loss and postural hypotension. A 9 am cortisol result has returned at 150 nmol/l.

What is the most appropriate interpretation of this result?

	Inconclusive result - should be repeated	4%
	Confirms a diagnosis of Addison's disease	12%
🟥	Confirms a diagnosis of Conn's disease	2%
🟩	Inconclusive result - should be referred for short Synacthen test	73%
	Excludes a diagnosis of Addison's disease	9%

9 am cortisol between 100-500nmol/l is inconclusive and requires further investigation with a short synacthen test

Important for me Less important

The correct answer is that this is an inconclusive result and the patient should be further investigated with a short Synacthen test. 9 am cortisol results between 100-500nmol/l are inconclusive and patients should be referred to secondary care for further investigation. A result less than 100nmol/l makes Addison's disease or hypoadrenalism likely, whilst a result >500nmol/l makes a diagnosis of Addison's disease very unlikely.

Simply repeating the test would not be the correct answer unless there was concern that the test was not taken at the correct time.

A result of 150nmol/l would not confirm a diagnosis of Addison's disease. A result <100nmol/l would suggest a definite abnormality but the definitive investigation is a short Synacthen test.

A 9 am cortisol of 150nmol/l would not confirm a diagnosis of Conn's syndrome. Whilst 9 am cortisol can be useful in the diagnosis of Conn's, patients typically require plasma renin:aldosterone level.

A 9 am cortisol above 500nmol/l not below would make a diagnosis of Addison's very unlikely.

Discuss (8) Improve

Next question

Addison's disease: investigations ★

In a patient with suspected Addison's disease the definite investigation is an ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If an ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:

- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:

- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

Next question

Textbooks

High-yield textbook

PassMedicine

← Question 396 of 414 ✗ ⚐ →

Which one of the following statements regarding impaired glucose regulation is correct?

	All patient should have a repeat oral glucose tolerance test every 2 years	5%
🟩	Patients with impaired glucose tolerance are more likely to develop diabetes than patients with impaired fasting glycaemia	54%
🟥	Impaired glucose tolerance (IGT) is defined as a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l	25%
	Around 1 in 20 adults in the UK have impaired glucose regulation	13%
	Patients should be offered pioglitazone if lifestyle changes fail to improve their glucose profile	3%

The correct answer is: **Patients with impaired glucose tolerance are more likely to develop diabetes than patients with impaired fasting glycaemia**. This statement is accurate as it reflects the current understanding of the progression of diabetes. Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are both pre-diabetic states, but IGT has been shown to have a higher risk for progression to diabetes compared to IFG. This might be due to differences in insulin resistance and beta-cell function.

The first option, **All patient should have a repeat oral glucose tolerance test every 2 years**, is incorrect. While monitoring blood glucose levels in at-risk individuals is important, there's no universal guideline that recommends repeating an oral glucose tolerance test every two years for all patients. The frequency of testing should be individualised based on each patient's risk factors and clinical condition.

The third statement, **Impaired glucose tolerance (IGT) is defined as a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l**, is also incorrect. It describes the criteria for diagnosing impaired fasting glycaemia (IFG), not IGT. IGT is diagnosed when the 2-hour post-load plasma glucose level during an oral glucose tolerance test is between 7.8 and 11.0 mmol/l.

The fourth option, **Around 1 in 20 adults in the UK have impaired glucose regulation**, may seem plausible but this figure does not accurately reflect the prevalence of impaired glucose regulation in the UK adult population which varies widely depending on age group, ethnicity and other risk factors.

Lastly, **Patients should be offered pioglitazone if lifestyle changes fail to improve their glucose profile**, while pioglitazone can indeed help improve glycemic control in some cases, it's not typically the first-line treatment recommended if lifestyle modifications fail to manage prediabetes effectively according to NICE guidelines in the UK which recommend metformin as a pharmacological intervention following lifestyle changes failure.

👍 👎 Discuss (7) Improve

Next question

Prediabetes and impaired glucose regulation ★

Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. The term includes patients who have been labelled as having either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes. Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.

Terminology

- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

Identification of patients with prediabetes

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

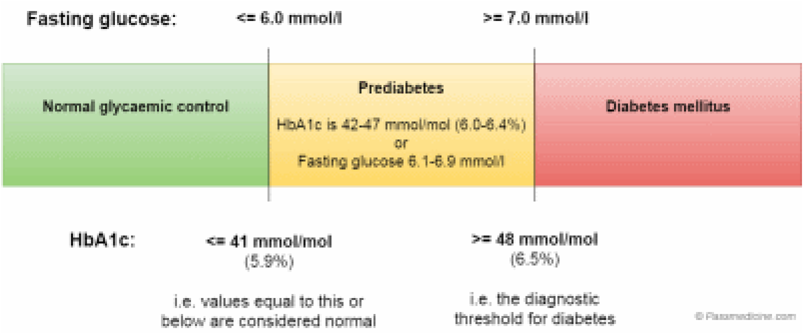
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

Management
- lifestyle modification: weight loss, increased exercise, change in diet
- at least yearly follow-up with blood tests is recommended
- NICE recommend metformin for adults at high risk '*whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme*'

Impaired fasting glucose and impaired glucose tolerance

There are two main types of IGR:
- impaired fasting glucose (IFG) - due to hepatic insulin resistance
- impaired glucose tolerance (IGT) - due to muscle insulin resistance
- patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Definitions
- a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)
- impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- people with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT

Next question

PassMedicine

Question 397 of 414 ✗

A middle-aged man with type 2 diabetes mellitus is reviewed. Despite weight loss, metformin and gliclazide his HbA1c is 68 mmol/mol (8.4%). The patient agrees to start insulin therapy. According to NICE guidelines which type of insulin should be tried initially?

	Basal bolus regime	36%
🟩	Isophane (NPH insulin)	35%
	Biphasic insulin	13%
🟥	Glargine	13%
	Detemir	3%

From NICE Clinical Knowledge Summaries:

> *The National Institute for Health and Care Excellence (NICE) recommends that in adults with type 2 diabetes:*
>
> - *Neutral Protamine Hagedorn (NPH) insulin [also known as isophane insulin] (injected once or twice daily according to need) should be offered.*
> - *NPH plus a short-acting insulin should be considered (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher). This may be administered either separately or as a pre-mixed (biphasic) human insulin preparation.*
> - *Insulin detemir or insulin glargine should be considered as an alternative to NPH insulin if:*
> - *→ The person needs assistance from a carer or healthcare professional to inject insulin and the use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily, or*
> - *→ The person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or*
> - *→ The person would otherwise need twice-daily NPH insulin injections in combination with oral antidiabetic drugs.*

👍 👎 Discuss (10) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice

- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

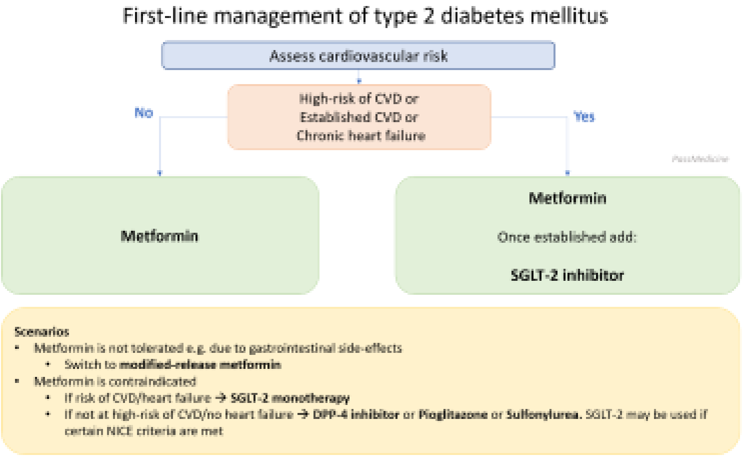
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor

Scenarios

- Metformin is not tolerated e.g. due to gastrointestinal side-effects
  - Switch to **modified-release metformin**
- Metformin is contraindicated
  - If risk of CVD/heart failure → **SGLT-2 monotherapy**
  - If not at high-risk of CVD/no heart failure → **DPP-4 inhibitor** or **Pioglitazone** or **Sulfonylurea.** SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset

- if standard-release metformin is not tolerated then modified-release metformin should be trialled

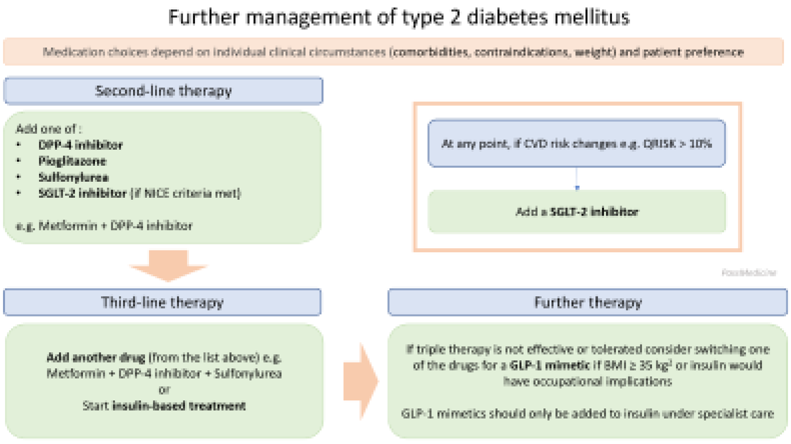
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
    - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
    - the patient has established CVD
    - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
    - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
    - DPP-4 inhibitor or pioglitazone or a sulfonylurea
    - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
PassMedicine
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or
- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

GLP-1 mimetics should only be added to insulin under specialist care

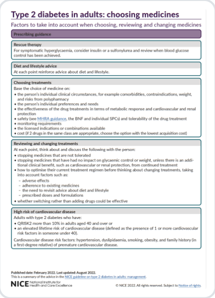
Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)

- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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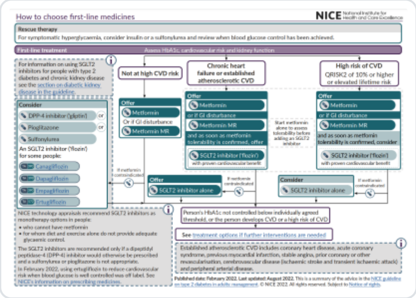

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk

Offer: Metformin. Or if GI disturbance: Metformin MR

Chronic heart failure or established atherosclerotic CVD

Offer: Metformin; or if GI disturbance: Metformin MR; and as soon as metformin tolerability is confirmed, offer: SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD

QRISK2 of 10% or higher or elevated lifetime risk

Offer: Metformin; or if GI disturbance: Metformin MR; and as soon as metformin tolerability is confirmed, consider: SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated — Consider: DPP-4 inhibitor ('gliptin') or Pioglitazone or Sulfonylurea. An SGLT2 inhibitor ('flozin') for some people: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

If metformin contraindicated — Offer: SGLT2 inhibitor alone

If metformin contraindicated — Consider: SGLT2 inhibitor alone

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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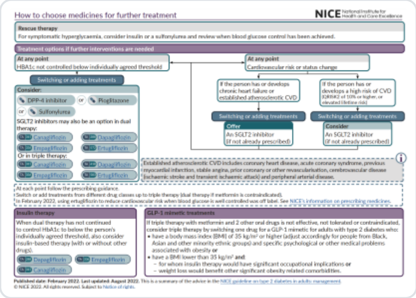

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider: DPP-4 inhibitor or Pioglitazone or Sulfonylurea

SGLT2 inhibitors may also be an option in dual therapy: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

Or in triple therapy: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD — Switching or adding treatments — Offer: An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk) — Switching or adding treatments — Consider: An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

Dapagliflozin, Empagliflozin, Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m² or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m² **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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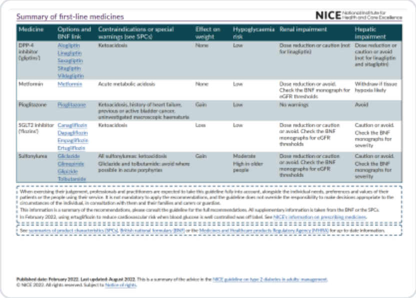

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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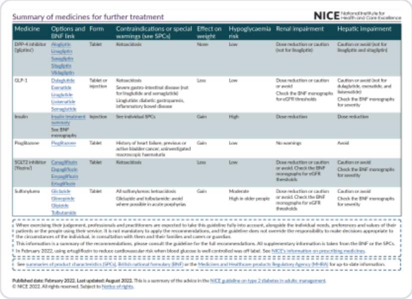

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)

- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
    - an ARB is preferred if the patient has a black African or African-Caribbean family origin

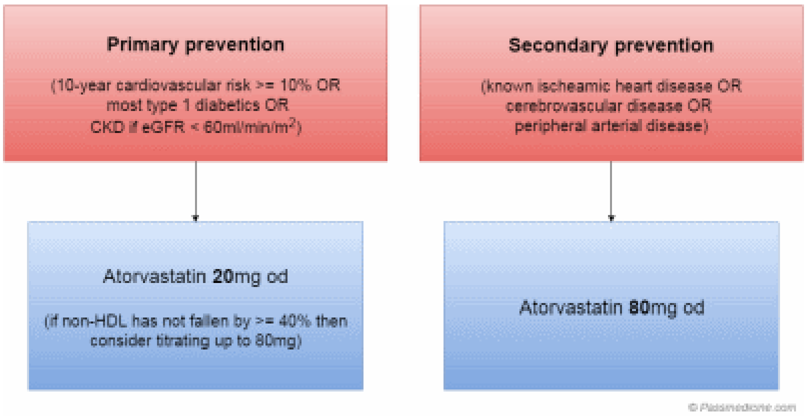
	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m²)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
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Graphic showing choice of statin.

Next question

Textbooks

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Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

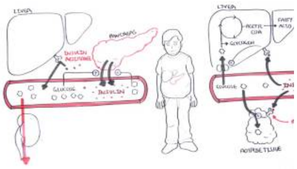
2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

Report broken link

Media



Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3

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Question 398 of 414 ✗

A 24-year-old woman presents to the emergency department with sweating, palpitations and hypertension. She describes a recent history of recurrent headaches.

On examination, she appears generally unwell and has a blood pressure of 177/87 mmHg. A small mass is palpable over the anterior neck. She is noted to have arachnodactyly, scoliosis and examination of the mouth reveals a high-arched palate.

Blood tests are performed and demonstrate hypokalaemia.

What is the most likely diagnosis?

	Multiple endocrine neoplasia type I	12%
🟥	Multiple endocrine neoplasia type IIa	21%
🟩	Multiple endocrine neoplasia type IIb	55%
	Neurofibromatosis	3%
	Von Hippel-Lindau syndrome	10%

Medullary thyroid cancer, phaeochromocytoma, marfanoid body habitus - multiple endocrine neoplasia type IIb

Important for me Less important

The diagnosis here is multiple endocrine neoplasia (MEN) type IIb. Hypertension, hypokalaemia, sweating and palpitations in a young patient allude to a phaeochromocytoma. Whilst this is found in both types IIa and IIb, as is medullary thyroid cancer - hinted at by the neck mass - the marfanoid body features described here are only found in type IIb.

MEN type I is incorrect. This is not associated with phaeochromocytoma, but with hyperparathyroidism due to parathyroid hyperplasia, pituitary tumours and pancreatic tumours. These other features are not seen in this patient.

MEN type IIa is incorrect. Although there is some overlap with type IIb with the presence of phaeochromocytoma and medullary thyroid cancer, marfanoid features would not be present in

MEN type IIa. Hyperparathyroid signs would also have been hinted at, as this is found in type IIa.

Neurofibromatosis - specifically, type I - is associated with phaeochromocytomas. However, the other features are not present in the patient - cafe-au-lait spots, axillary and groin freckles, neurofibromas, scoliosis and iris hamartomas.

Von Hippel-Lindau syndrome is a condition with a number of neoplastic predispositions - including phaeochromocytoma. Other neoplasms include cerebellar and retinal haemangiomas, endolymphatic sac tumours and clear-cell renal cell carcinoma. There are no signs of these in this patient.

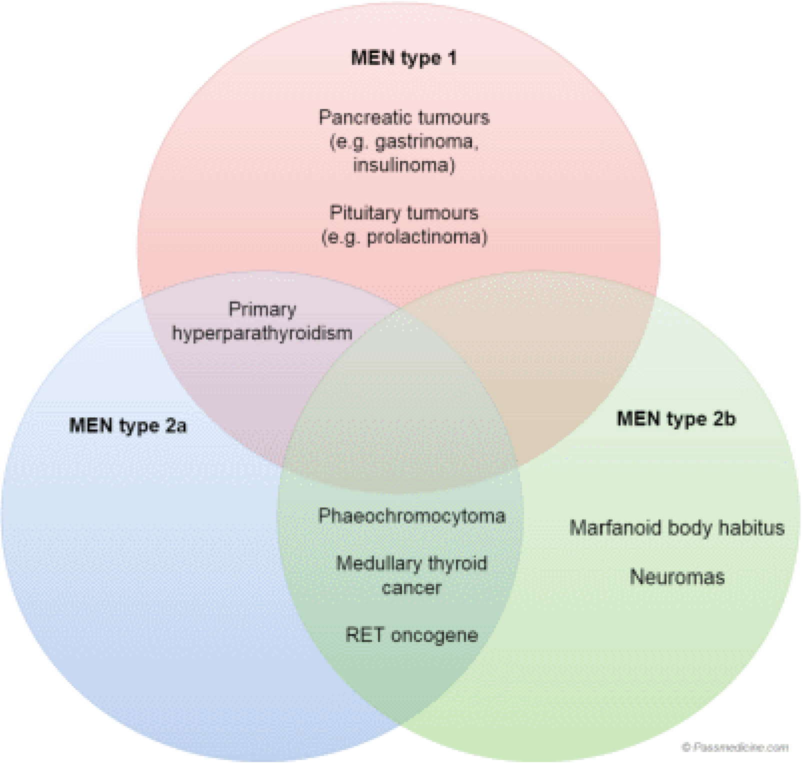
👍 👎 Discuss (3) Improve

Next question

Multiple endocrine neoplasia ★

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

MEN type I	**MEN type IIa**	**MEN type IIb**
3 **P**'s **P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia **P**ituitary (70%) **P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration) Also: adrenal and thyroid	Medullary thyroid cancer (70%) 2 **P**'s **P**arathyroid (60%) **P**haeochromocytoma	Medullary thyroid cancer 1 **P** **P**haeochromocytoma Marfanoid body habitus Neuromas
MEN1 gene Most common presentation = hypercalcaemia	RET oncogene	RET oncogene


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
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Venn diagram showing the different types of MEN and their associated features

Next question

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Pancreatic Neuroendocrine Neoplasms

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Question 399 of 414 ✗

A 49-year-old man comes into clinic. One of his friends has recently had a myocardial infarction and he is concerned about his own risk of coronary heart disease. He has no past medical history of note other than anxiety for which he is not currently taking any medication. He does however smoke around 20 cigarettes a day. Cardiovascular examination is unremarkable. His BMI is 26 kg/m^2 and blood pressure is 126/82 mmHg.

You strongly advise him to stop smoking. What is the most appropriate further course of action?

	Reassure him that he has a very low risk of coronary heart disease given his age	7%
	Arrange a 24 hour blood pressure monitor	1%
🟩	Arrange a lipid profile then calculate his QRISK2 score	88%
🟥	Start orlistat	2%
	Refer him for an exercise tolerance test	2%

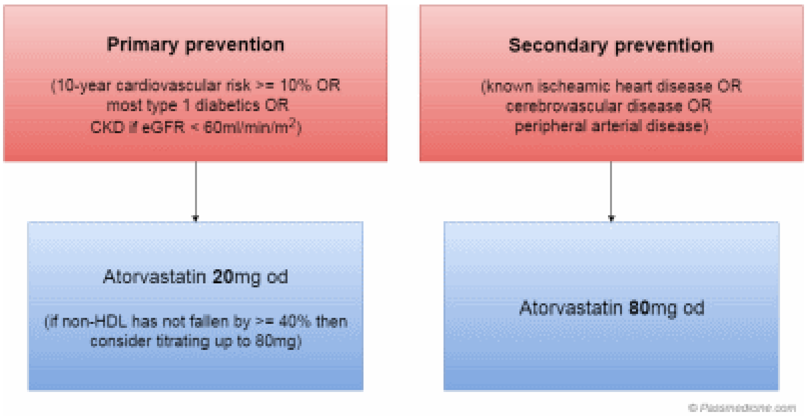
If we feed his age, gender and smoking history into QRISK2 this gives a 10-year-risk of cardiovascular disease (CVD) of 13.9%. He is therefore an appropriate person to have a 'formal' assessment of CVD risk using a lipid profile to further inform the QRISK2 score.

Discuss (7) | Improve

Next question

Hyperlipidaemia: management

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.


Primary prevention
(10-year cardiovascular risk >= 10% OR
most type 1 diabetics OR
CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischaemic heart disease OR
cerebrovascular disease OR
peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then
consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Primary prevention - who and how to assess risk

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

Measuring lipid levels

When measuring lipids both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples do not need to be fasting.

In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool. If however, the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if:

- the total cholesterol level greater than 7.5 mmol/L and/or
- there is a personal or family history of premature coronary heart disease (an event before 60 years in an index person or first-degree relative [parents, siblings, children])

Interpreting the QRISK2 result

Probably the headline change in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

Special situations

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD
- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

Secondary prevention

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

Follow-up of people started on statins

NICE recommend we follow up patients at 3 months
- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

Lifestyle modifications

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet
- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity
- each week aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation: men and women are advised not to drink more than 14 units a week on a regular basis

Smoking cessation

- smokers should be encouraged to quit

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 9 👎 6

2014 Lipid modification guidelines

Clinical Knowledge Summaries 👍 4 👎 3

Managing lipids in type 2 diabetes

Report broken link

PassMedicine

← Question 400 of 414 ✕ ⚑ →

What chromosome abnormality is associated with Klinefelter's syndrome?

	47, XO	4%
🟩	47, XXY	73%
🟥	46, XXY	15%
	47, XYY	6%
	47, XXO	2%

Klinefelter's - 47, XXY

Important for me Less important

👍 👎 Discuss (1) Improve

Next question

Klinefelter's syndrome ★

Klinefelter's syndrome is associated with karyotype 47, XXY.

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels but low testosterone

PassMedicine

Question 401 of 414 ✗

A 67-year-old man who has a history of type 2 diabetes mellitus and benign prostatic hypertrophy presents with burning pain in his feet. This has been present for the past few months and is getting gradually worse. He has tried taking duloxetine but unfortunately has received no benefit. Clinical examination is unremarkable other than diminished sensation to fine touch on both soles. What is the most suitable initial management?

	Carbamazepine	3%
	Amitriptyline	38%
🟩	Pregabalin	56%
🟥	Fluoxetine	3%
	Sodium valproate	1%

Amitriptyline would normally be first choice but given his history of benign prostatic hyperplasia it is better to avoid amitriptyline due to the risk of urinary retention.

Discuss (2) Improve

Next question

Diabetic neuropathy

Peripheral neuropathy

Diabetes typically leads to sensory loss and not motor loss. Sensory loss typically results in a 'glove and stocking' distribution, with the lower legs affected first due to the length of the sensory neurons supplying this area. Painful diabetic neuropathy is also a common problem in clinical practice.

NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first line treatment: amitriptyline, duloxetine, gabapentin or pregabalin

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

Gastrointestinal autonomic neuropathy

Gastroparesis

- occurs secondary to autonomic neuropathy
- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

Chronic diarrhoea

- often occurs at night

Gastro-oesophageal reflux disease

- caused by decreased lower esophageal sphincter (LES) pressure

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 2 👎 0

2013 Neuropathic pain guidelines

PassMedicine

← Question 402 of 414 ✗ ⚑ →

Each one of the following causes of hyponatraemia is associated with a urinary sodium of less than 20 mmol/L, except:

	Diarrhoea	9%
	Psychogenic polydipsia	15%
	Burns	6%
🟥	Secondary hyperaldosteronism	12%
🟩	Syndrome of inappropriate ADH	58%

Syndrome of inappropriate ADH is associated with urinary sodium > 20 mmol/l

👍 👎 Discuss (4) Improve

Next question

Hyponatraemia ★

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis

Urinary sodium > 20 mmol/l

Sodium depletion, renal loss (patient often hypovolaemic)

- diuretics: thiazides, loop diuretics
- Addison's disease
- diuretic stage of renal failure

Patient often euvolaemic

- SIADH (urine osmolality > 500 mmol/kg)

- hypothyroidism

Urinary sodium < 20 mmol/l

Sodium depletion, extra-renal loss
- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)
- secondary hyperaldosteronism: heart failure, liver cirrhosis
- nephrotic syndrome
- IV dextrose
- psychogenic polydipsia

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Royal College of Physicians 👍 5 👎 2

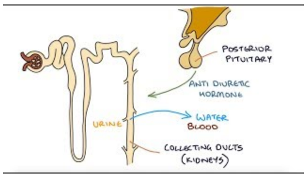
2017 Hyponatraemia â€“ presentations and management

European Society of Endocrinology 👍 6 👎 4

2014 Guidelines on diagnosis and treatment of hyponatraemia

Report broken link

Media


POSTERIOR PITUITARY
ANTI DIURETIC HORMONE
URINE
WATER
BLOOD
COLLECTING DUCTS (KIDNEYS)

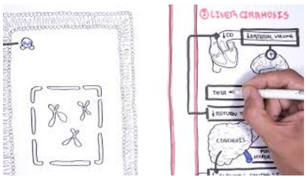
Understanding Hyponatraemia

Zero To Finals - YouTube 👍 68 👎 3

WHAT IS...
SIADH?

Syndrome of inappropriate antidiuretic hormone (SIADH)

Osmosis - YouTube 👍 9 👎 2


LIVER CIRRHOSIS

Hyponatraemia - classification, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 8 👎 2

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Score: **22.4%**

1 ✓
2 ✓
3 ✓
4 ✗
5 ✗
6 ✗
7 ✗
8 ✗

PassMedicine

← Question 403 of 414 ✗ →

A 52-year-old man presents for review at the Endocrinology clinic. He has a history of congestive cardiac failure and type 2 diabetes mellitus, for which he is currently taking modified-release metformin. His latest HbA1c reading is 55mmol/mol, and he agrees to start on gliclazide.

What possible side-effect should he be counselled about for this medication?

	Euglycaemic ketoacidosis	5%
	Fluid retention	5%
	Increased risk of urinary tract infections	3%
🟩	Weight gain	83%
🟥	Weight loss	4%

Sulfonylureas often cause weight gain

Important for me Less important

The correct answer is **weight gain**. Sulfonylureas such as gliclazide are known to cause weight gain. This is because they directly increase the amount of insulin secreted by the pancreas, which in turn stimulates cells to store glucose in the form of fat.

Euglycaemic ketoacidosis is incorrect as this is a side-effect of SGLT2 inhibitors such as dapagliflozin.

Fluid retention is incorrect. Fluid retention is a side-effect of thiazolidinediones such as pioglitazone, which would be unlikely to be recommended in this patient with congestive cardiac failure.

Increased risk of urinary tract infections is incorrect. This is a side-effect of SGLT2 inhibitors, which inhibit glucose reuptake in the kidney. This increases the concentration of glucose in the urine and creates a favourable environment for bacterial growth.

Weight loss is incorrect as sulfonylureas tend to cause weight gain for the reasons described above.

Discuss (2) Improve

Next question

Sulfonylureas

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K^+(K_{ATP}) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

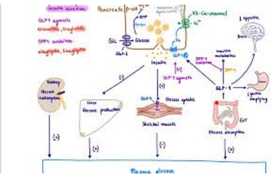
Next question

Textbooks

High-yield textbook

Extended textbook

Media



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 34 👎 10

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 12 👎 5

Report broken media

Score: **22.3%**

1	✓
2	✓
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401	✗
402	✗
403	✗

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Question 404 of 414 ✗

Which one of the following is least associated with hypercalcaemia?

Sarcoidosis	3%
Primary hyperparathyroidism	3%
Thiazide diuretics	24%
Squamous cell lung cancer	9%
Monoclonal gammopathy of uncertain significance	60%

One of the key differentiating features between monoclonal gammopathy of uncertain significance (MGUS) and myeloma is the absence of complications such as immune paresis, hypercalcaemia and bone pain

Discuss (4) | Improve

Next question

Hypercalcaemia: causes

Two conditions account for 90% of cases of hypercalcaemia:

- 1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
- 2. Malignancy: the commonest cause in hospitalised patients. This may be due to a number of processes, including;
  - PTHrP from the tumour e.g. squamous cell lung cancer
  - bone metastases
  - myeloma,: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- for this reason, measuring parathyroid hormone levels is the key investigation for patients with hypercalcaemia

Other causes include

- sarcoidosis
  - other causes of granulomas may lead to hypercalcaemia e.g. tuberculosis and histoplasmosis
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs:
  - thiazides
  - calcium-containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone
  - usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

Next question

Textbooks

High-yield textbook

Extended textbook

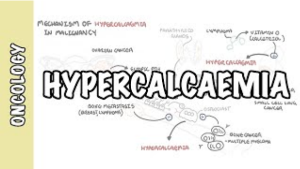
Links

Royal College of Physicians 👍 9 👎 1

Hypercalcaemia â€“ presentation and management

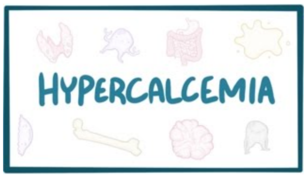
Report broken link

Media


ONCOLOGY
MECHANISM OF HYPERCALCAEMIA IN MALIGNANCY
HYPERCALCAEMIA

Hypercalcemia in malignancy

Armando Hasudungan - YouTube 👍 19 👎 2


HYPERCALCEMIA

Hypercalcemia

Osmosis - YouTube 👍 18 👎 7

Report broken media

Score: **22.3%**

1	✓
2	✓
3	✓
4	✗
5	✗
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12	✓
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14	✓
15	✗
16	✗
17	✓

PassMedicine

Question 405 of 414 ✗

Which one of the following features is least associated with primary hyperparathyroidism?

	Depression	6%
🟥	Polydipsia	5%
🟩	Sensory loss	51%
	Peptic ulceration	15%
	Hypertension	24%

The correct answer is **Sensory loss**. Primary hyperparathyroidism is a condition characterised by overactivity of the parathyroid glands, leading to increased secretion of parathyroid hormone (PTH). This results in elevated levels of calcium in the blood, known as hypercalcaemia. Sensory loss is not typically associated with this condition as PTH does not directly affect the nervous system and its sensory pathways.

Depression is indeed associated with primary hyperparathyroidism. Although the exact mechanism remains unclear, it's believed that high calcium levels can impact brain function and mood regulation. Studies have shown that patients suffering from primary hyperparathyroidism often experience depressive symptoms which tend to improve following parathyroidectomy.

Polydipsia, or excessive thirst, is another symptom seen in primary hyperparathyroidism. This occurs as a result of hypercalcaemia causing dehydration due to increased urinary frequency (polyuria), which in turn triggers thirst mechanisms in the body.

Peptic ulceration can also be associated with primary hyperparathyroidism. Hypercalcaemia stimulates gastrin secretion which increases gastric acid production leading to peptic ulcers. However, this association has been less evident since the discovery and widespread use of Helicobacter pylori eradication therapy for peptic ulcer disease.

Finally, **Hypertension** has been reported in some patients with primary hyperparathyroidism. The mechanism is not completely understood but may involve increased intracellular calcium leading to vascular smooth muscle contraction and thus raising blood pressure. However, it's important to note that hypertension can have many other causes and its presence should prompt further investigation rather than assuming it's due to primary hyperparathyroidism alone.

👍 | 👎 | Discuss (3) | Improve

Next question

Primary hyperparathyroidism ★

Primary hyperparathyroidism is caused by excess secretion of PTH resulting in hypercalcaemia. It is the most common cause of hypercalcaemia in outpatients and is often diagnosed following an incidental finding of an elevated serum calcium concentration. In 85% of cases a parathyroid adenoma is responsible.

Causes of primary hyperparathyroidism
- 85%: solitary adenoma
- 10%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

Around 80% of patients are asymptomatic and are diagnosed on routine blood tests. The symptomatic features of primary hyperparathyroidism may be remembered by the mnemonic: 'bones, stones, abdominal groans and psychic moans':
- polydipsia, polyuria
- depression
- anorexia, nausea, constipation
- peptic ulceration
- pancreatitis
- bone pain/fracture
- renal stones
- hypertension

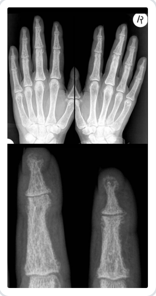
Associations
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations
- bloods
    - raised calcium, low phosphate

  - PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- x-ray findings
  - pepperpot skull
  - osteitis fibrosa cystica

Treatment

- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- patients not suitable for surgery may be treated with cinacalcet, a calcimimetic
  - a calcimimetic 'mimics' the action of calcium on tissues by allosteric activation of the calcium-sensing receptor



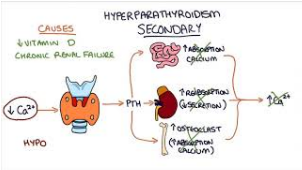
Next question

Textbooks

High-yield textbook

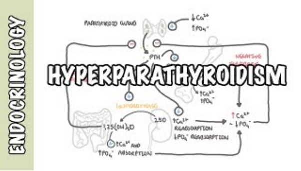
Extended textbook

Media


HYPERPARATHYROIDISM
SECONDARY
CAUSES
↓ VITAMIN D
CHRONIC RENAL FAILURE
↓ Ca2+
HYPO
PTH
↑ ABSORPTION CALCIUM
↑ REABSORPTION (↓ SECRETION)
↑ OSTEOCLAST (↑ ABSORPTION CALCIUM)
↑ Ca2+

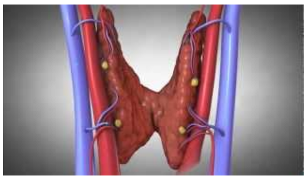
Understanding Hyperparathyroidism

Zero to Finals - YouTube 👍 70 👎 2


ENDOCRINOLOGY
HYPERPARATHYROIDISM

Hyperparathyroidism and the different types, causes, pathophysiology, treatment

Armando Hasudungan - YouTube 👍 21 👎 2



Parathyroid Glands and Hyperparathyroidism

Norman Parathyroid Center - YouTube 👍 20 👎 5

Report broken media

Score: **22.2%**

1 ✓
2 ✓
3 ✓
4 ✗
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11 ✗

PassMedicine

Question 406 of 414 ✗

A 66-year-old man attends the endocrinology clinic for a review of his type 2 diabetes mellitus, which has been historically difficult to control. He also has a history of hypertension and hyperlipidaemia. He currently takes ramipril, atorvastatin, metformin, gliclazide and dapagliflozin.

On examination, he appears generally well. His BMI is 38 kg/m ^{2}. A recent blood test is shown below:

HbA1c	69 mmol/mol	(< 48)

What is the most appropriate next step?

Add insulin	23%
🟥 Add linagliptin	13%
Add pioglitazone	4%
🟩 Switch gliclazide for exenatide	56%
Switch gliclazide for pioglitazone	5%

TD2M: if a triple combination of drugs has failed to reduce HbA1c then switching one of the drugs for a GLP-1 mimetic is recommended, particularly if the BMI > 35

Important for me Less important

NICE guidelines take a stepwise approach to managing type 2 diabetes mellitus. This patient is currently on triple therapy. Despite this, his HbA1c is inadequately controlled. At this stage, the most appropriate next step is to switch one of the existing drugs for a glucagon-like peptide-1 (GLP-1) mimetic. This patient's BMI is over 35 kg/m ^{2} and he has other medical problems that would benefit from a reduction in weight - hypertension and hyperlipidaemia. As such, he should **switch from gliclazide to exenatide**. NICE guidelines recommend that metformin should be continued, and that dapagliflozin is beneficial for patients with cardiovascular risk factors (this patient has hyperlipidaemia). Gliclazide can cause weight gain which would be undesirable and is therefore the most appropriate drug to discontinue, in favour of exenatide.

Adding insulin is incorrect. Whilst starting insulin is not an unreasonable option here, and a suitable alternative to a GLP-1 mimetic, it would be unwise to continue all of the existing drugs alongside insulin. At the very least, it would be prudent to discontinue gliclazide, given the increased risk of hypoglycaemia.

Adding linagliptin is incorrect. This is a DPP-4 inhibitor. Whilst it may have been appropriate as part of the initial triple therapy, it should not be added as a fourth agent.

Adding pioglitazone is incorrect. This is a suitable second- or third-line option. However, as this patient is already on triple therapy for his diabetes, one of the current drugs should now be swapped for a GLP-1 mimetic. NICE guidelines suggest using a GLP-1 mimetic at this stage, rather than a DPP-4 inhibitor such as pioglitazone, as the latter is unlikely to be as effective. The GLP-1 mimetic will also provide additional benefits with regards to weight loss.

Switching gliclazide for pioglitazone is incorrect. At this stage, it is more suitable to swap gliclazide for a GLP-1 mimetic, as per NICE guidelines.

👍 👎 Discuss Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	HbA1c target
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

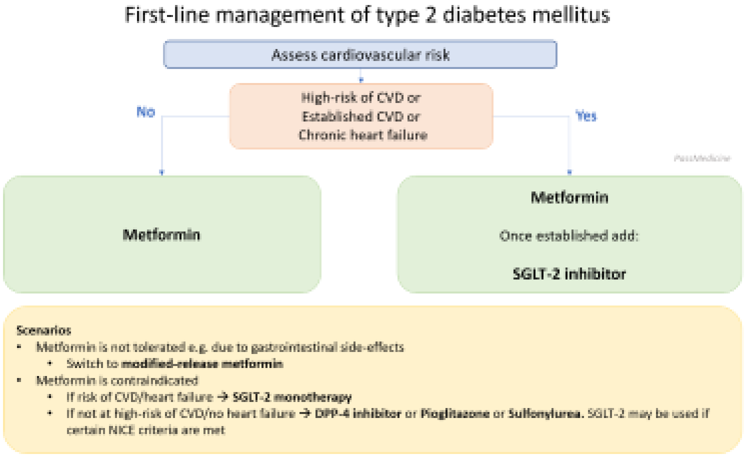
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	HbA1c target
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor
Scenarios
Metformin is not tolerated e.g. due to gastrointestinal side-effects
Switch to modified-release metformin
Metformin is contraindicated
If risk of CVD/heart failure → SGLT-2 monotherapy
If not at high-risk of CVD/no heart failure → DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

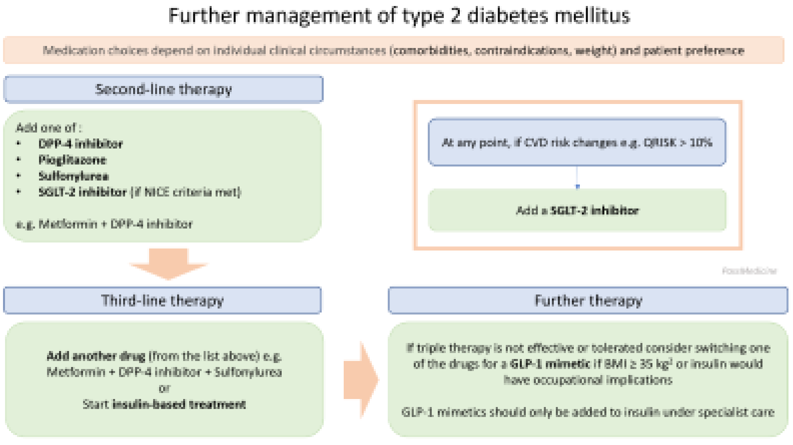
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
    - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
    - the patient has established CVD
    - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
    - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
    - DPP-4 inhibitor or pioglitazone or a sulfonylurea
    - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met



Further management of type 2 diabetes mellitus

Medication choices depend on individual clinical circumstances (**comorbidities, contraindications, weight) and patient preference**

Second-line therapy

Add one of :
- **DPP-4 inhibitor**
- **Pioglitazone**
- **Sulfonylurea**
- **SGLT-2 inhibitor** (if NICE criteria met)

e.g. Metformin + DPP-4 inhibitor

At any point, if CVD risk changes e.g. QRISK > 10%

Add a **SGLT-2 inhibitor**

Third-line therapy

Add another drug (from the list above) e.g.
Metformin + DPP-4 inhibitor + Sulfonylurea
or
Start **insulin-based treatment**

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a **GLP-1 mimetic** if BMI ≥ 35 kg^2 or insulin would have occupational implications

GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:
- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:
- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:
- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

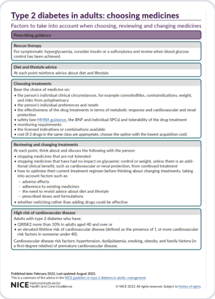
GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice

At each point reinforce advice about diet and lifestyle.

Choosing treatments

Base the choice of medicine on:

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments

At each point, think about and discuss the following with the person:

- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

Published date: February 2022. Last updated: August 2022.
This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.
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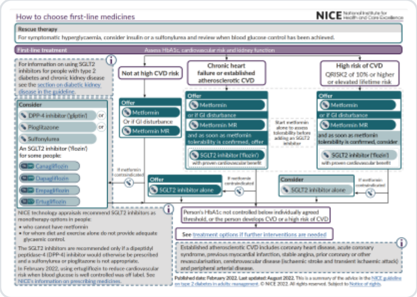

How to choose first-line medicines NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR

Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated
Offer
SGLT2 inhibitor alone

If metformin contraindicated
Consider
SGLT2 inhibitor alone

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:

- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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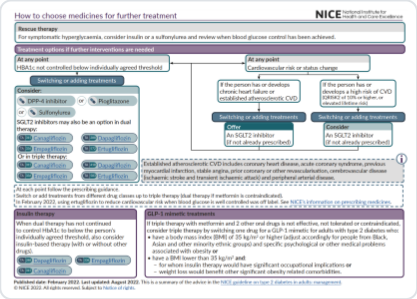

How to choose medicines for further treatment NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments
Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin
Or in triple therapy:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin
Empagliflozin
Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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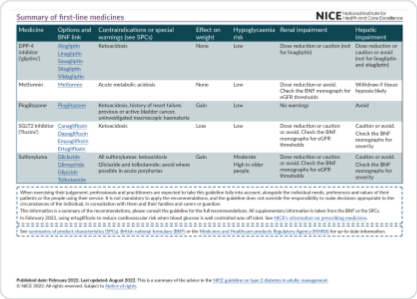

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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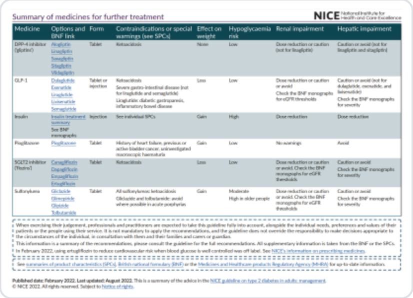

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

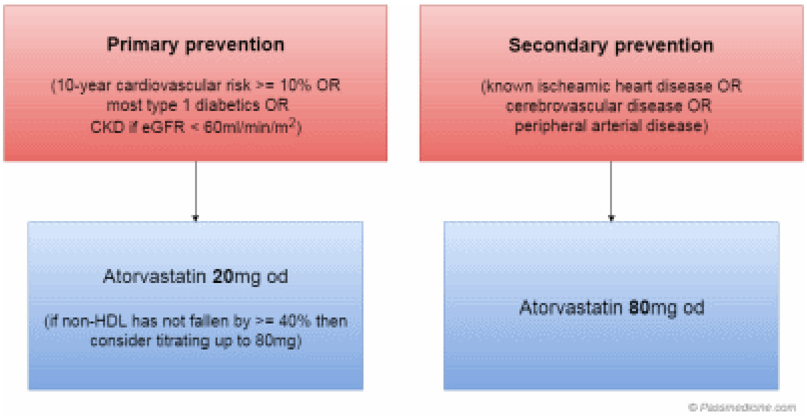
	Clinic BP	**ABPM / HBPM**
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m^2)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin **20**mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin **80**mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

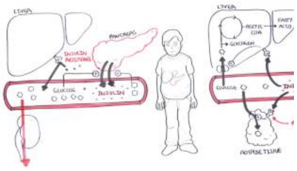
NICE

2022 Type 2 diabetes guidelines

👍 8 👎 5

Report broken link

Media

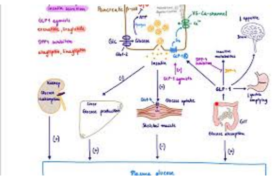


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

Report broken media

Score: **22.2%**

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PassMedicine

Question 407 of 414 ✓

A 29-year-old woman has just found out she is pregnant for the second time. Her first pregnancy was complicated by gestational diabetes. Following her first pregnancy she was told she was no longer diabetic. What is the most appropriate management?

Check HbA1c immediately	5%
Start metformin and ask the woman to self-monitor glucose	4%
Do oral glucose tolerance test as soon as possible after booking	58%
Do oral glucose tolerance test at 16-18 weeks	19%
Do oral glucose tolerance test at 24-28 weeks	14%

NICE have recently updated their guidelines. Women who are at risk of gestational diabetes should have an oral glucose tolerance test as soon as possible after booking, rather than waiting to 16-18 weeks as was previously advocated.

Discuss (5) Improve

Next question

Gestational diabetes

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimates the following breakdown:

- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Gestational diabetes

Gestational diabetes is the second most common medical disorder complicating pregnancy (after hypertension), affecting around 4% of pregnancies.

Risk factors for gestational diabetes

- BMI of > 30 kg/m²
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes

- the oral glucose tolerance test (OGTT) is the test of choice
- women who've previously had gestational diabetes: OGTT should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes

- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/L
- 2-hour glucose is >= 7.8 mmol/L

Management of gestational diabetes

- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about self-monitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol/l a trial of diet and exercise should be offered
    - if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
    - if glucose targets are still not met insulin should be added to diet/exercise/metformin
    - gestational diabetes is treated with short-acting, not long-acting, insulin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered
- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes

- weight loss for women with BMI of > 27 kg/m^2

- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or:
2 hour after meals	6.4 mmol/l

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Postgraduate Medical Journal 👍 2 👎 2

DKA in pregnancy

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PassMedicine

Question 408 of 414 ✗

Which one of the following is not a recognised cause of hypocalcaemia?

	Hypoparathyroidism	4%
🟩	Bendroflumethiazide	46%
	Pseudohypoparathyroidism	15%
🟥	Acute pancreatitis	12%
	Acute rhabdomyolysis	22%

The correct answer is **Bendroflumethiazide**. Bendroflumethiazide is a thiazide diuretic used in the treatment of hypertension and oedema. It does not cause hypocalcaemia, but instead it can lead to hypercalcaemia due to increased renal calcium reabsorption.

Hypoparathyroidism is an incorrect option as it is indeed a recognised cause of hypocalcaemia. Hypoparathyroidism refers to underactivity of the parathyroid glands resulting in reduced production of parathyroid hormone (PTH). PTH plays a crucial role in regulating blood calcium levels by increasing renal calcium reabsorption, promoting conversion of vitamin D into its active form which enhances intestinal absorption of calcium and mobilising calcium from bone. Therefore, deficiency of PTH leads to hypocalcaemia.

Pseudohypoparathyroidism also leads to hypocalcaemia and thus is an incorrect option. This condition involves resistance to the action of PTH often due to genetic mutations affecting signalling pathways for PTH receptor. Despite normal or high levels of PTH, its effect on target organs is blunted leading to decreased release of calcium into the bloodstream resulting in hypocalcaemia.

Acute pancreatitis is another recognised cause of hypocalcaemia making it an incorrect choice. In acute pancreatitis, there can be saponification where released fatty acids bind with calcium ions forming insoluble soaps leading to fall in serum calcium levels. Moreover, inflammation associated with pancreatitis can lead to capillary leak syndrome causing loss of protein-bound calcium into extravascular space further contributing to hypocalcaemia.

Finally, **acute rhabdomyolysis** too can result in hypocalcaemia making it an incorrect option. Rhabdomyolysis refers to breakdown of skeletal muscle fibres releasing intracellular contents including myoglobin into circulation which can lead to acute kidney injury (AKI). In AKI there may be impaired renal function including dysregulated reabsorption leading to losses including that of calcium causing hypocalcaemia.

👍 👎 Discuss (4) Improve

Next question

Hypocalcaemia: causes and management ★

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes
- vitamin D deficiency (osteomalacia)
- chronic kidney disease
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion
- acute pancreatitis

Contamination of blood samples with EDTA may also give falsely low calcium levels.

Management
- severe hypocalcaemia (e.g. carpopedal spasm, tetany, seizures or prolonged QT interval) requires IV calcium replacement
  - the preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
  - intravenous calcium chloride is more likely to cause local irritation
  - ECG monitoring is recommended
- further management depends on the underlying cause

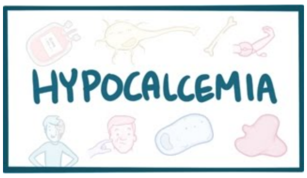
Next question

Textbooks

High-yield textbook

Extended textbook

Media



Hypocalcemia

Osmosis - YouTube 👍 20 👎 4

Report broken media

Score: **22.3%**

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374	✓

PassMedicine

Question 409 of 414 ✓

A 90-year-old man attends the hospital with progressive confusion over two weeks. His past medical history includes hypertension, diabetes, epilepsy and gallstones. His current medication includes doxazosin, bisoprolol, atorvastatin, levetiracetam, glimepiride, calcium and vitamin D.

A few months ago his GP started a low dose of doxazosin in the mornings as his blood pressure was 190/110 mmHg. The blood pressure is now well controlled. He thinks the queen is coming to visit him today. There is no focal neurology on examination.

Blood results are as follows:

Na^+	126 mmol/L	(135 - 145)
K^+	4.5 mmol/L	(3.5 - 5.0)
Urea	5 mmol/L	(2.0 - 7.0)
Creatinine	80 µmol/L	(55 - 120)

What is the most likely cause of the confusion?

Doxazosin	29%
Bisoprolol	3%
Atorvastatin	2%
Levetiracetam	27%
Glimepiride	38%

SIADH - drug causes: carbamazepine, sulfonylureas, SSRIs, tricyclics

Important for me Less important

The correct answer is glimepiride which is a sulfonylurea diabetic medication which is known to cause SIADH.

There are a number of distractors in the question. Blood pressure medications - alpha and beta blockers - do not classically cause SIADH but should be used with caution in elderly patients at risk of falls.

Statins do not cause SIADH or confusion. In elderly patients they can however be prone to myalgia and myositis due to drug interactions.

Levetiracetam is rarely associated with hyponatraemia.

👍 👎 Discuss (8) Improve

Next question

Syndrome of inappropriate ADH secretion ★

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention. Patients with SIADH are typically euvolemic, i.e. they do not show signs of overt volume depletion or overload.

Pathophysiology
- SIADH involves an excessive release of antidiuretic hormone (ADH), also known as vasopressin, which leads to water retention, volume expansion, and dilutional hyponatraemia
- ADH is produced by the hypothalamus and stored in the posterior pituitary gland. Its primary function is to regulate the body's water balance
- It does this by increasing water reabsorption in the collecting ducts of the kidneys, thereby decreasing the volume of urine produced
- In SIADH, there is an inappropriate and continuous release of ADH that is not inhibited by normal physiological mechanisms, such as adequate or excess body fluid levels
- As a result, the kidneys reabsorb more water, leading to decreased urine output, and expansion of extracellular fluid volume.
- Importantly, this increase in body fluid volume does not lead to the expected signs of fluid overload, such as oedema or hypertension, because the excess fluid is uniformly distributed throughout all body fluid compartments.
- However, as water is retained in the body, the concentration of electrolytes in the blood, particularly sodium, becomes diluted, leading to hyponatraemia.

Causes of SIADH

Category	Examples
Malignancy	• **small cell lung cancer** • also: pancreas, prostate

Category	**Examples**
Neurological	stroke subarachnoid haemorrhage subdural haemorrhage meningitis/encephalitis/abscess
Infections	tuberculosis pneumonia
Drugs	sulfonylureas* SSRIs, tricyclics carbamazepine vincristine cyclophosphamide
Other causes	positive end-expiratory pressure (PEEP) porphyrias

Investigations

- Urine osmolality: Urine osmolality is inappropriately high (>100 mOsm/kg) in relation to serum osmolality, as the kidneys should normally dilute urine in the setting of low serum osmolality.
- Urine sodium concentration: Urine sodium concentration is typically high (>40 mmol/L) due to the action of ADH on the renal tubules.

Management

- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

Next question

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PassMedicine

Question 410 of 414 ✗

A 26-year-old man is referred to the hypertension clinic after routine blood pressure monitoring recorded serial blood pressure readings as 180/100mmHg, 194/107mmHg and 195/106mmHg. He denies chest pain but has occasional frontal headaches and blurred vision. There is no family history of hypertension and he has no past medical history. He denies recreational drug use.

On examination, his chest is clear with normal heart sounds. His abdomen is soft and non-tender with no palpable organomegaly. Fundoscopy reveals mild arteriovenous nicking bilaterally.

Investigations:

Na^+	147 mmol/L	(135 - 145)
K^+	2.8 mmol/L	(3.5 - 5.0)
Urea	6.9 mmol/L	(2.0 - 7.0)
Creatinine	110 µmol/L	(55 - 120)

What is the next best investigation to order for this patient?

	Dexamethasone suppression test	9%
🟥	Renal artery angiography	4%
🟩	Renin:aldosterone ratio	70%
	Urinary metanephrines	14%
	IGF-1 level	3%

A plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism

Important for me Less important

This patient has severe hypertension. Primary hyperaldosteronism occurs secondary to excess aldosterone release that causes sodium retention, potassium loss, and hypertension. Primary hyperaldosteronism can be secondary to adrenal adenoma or bilateral adrenal hyperplasia and accounts for 5-10% of all cases of hypertension. The primary investigation is the plasma renin:

aldosterone ratio. Once primary hyperaldosteronism has been identified, treatment involves treating the cause with adrenal adenomas being surgically excised and bilateral adrenal hyperplasia being treated with aldosterone antagonists such as spironolactone.

A low-dose dexamethasone suppression test is a primary investigation to aid the diagnosis of Cushing's disease. Additional features of Cushing's syndrome include those of glucocorticoid excess such as proximal myopathy, abdominal striae, and thin skin.

IGF-1 levels are used to test for acromegaly, an endocrine disease secondary to excess growth hormone levels that stimulates soft tissue and skeletal growth. Hypertension is a feature of acromegaly. However, changes in appearance are also common including prognathism, spade-like hands, and with that, headaches, joint pains, and muscular weakness.

Renal artery angiography is used in the diagnosis of renal artery stenosis. Whilst it is a well-recognised cause of hypertension, it is less common in previously healthy and young males.

Urinary metanephrines are used in the diagnosis of phaeochromocytoma. A phaeochromocytoma is a rare tumour of the sympathetic nervous system, most of which arises in the adrenal medulla. These tumours secrete catecholamines, adrenaline, and noradrenaline and along with hypertension, additional symptoms include anxiety, tremor, sweating and flushing.

👍 👎 💬 Discuss (3) Improve

Next question

Primary hyperaldosteronism ★

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the most common cause. Differentiating between the two is important as this determines treatment.

Causes
- bilateral idiopathic adrenal hyperplasia: the cause of around 60-70% of cases
- adrenal adenoma: 20-30% of cases
- unilateral hyperplasia
- familial hyperaldosteronism
- adrenal carcinoma

Features

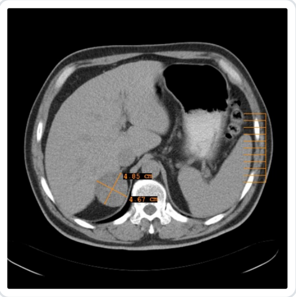
- **hypertension**
  - increasingly recognised but still underdiagnosed cause of hypertension
- **hypokalaemia**
  - e.g. muscle weakness
  - this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients, and is more common with adrenal adenomas
- metabolic alkalosis

Investigations

- guidelines vary but certain patients should be screened for primary hyperaldosteronism, e.g.
  - hypertension with hypokalemia
  - treatment-resistant hypertension
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
  - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
  - if the CT is normal adrenal venous sampling (AVS) can be used to distinguish between unilateral adenoma and bilateral hyperplasia

Management

- adrenal adenoma: surgery (laparoscopic adrenalectomy)
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



Next question

Textbooks

High-yield textbook

Extended textbook

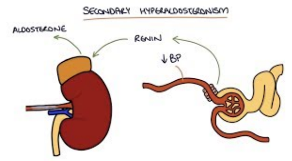
Links

The Endocrine Society 👍 5 👎 3

2016: The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment

Report broken link

Media


SECONDARY HYPERALDOSTERONISM
ALDOSTERONE
RENIN
↓BP

Hyperaldosteronism and Conn's Syndrome

Zero To Finals - YouTube 👍 47 👎 5

HYPERALDOSTERONISM

Hyperaldosteronism - causes, symptoms, diagnosis, treatment, pathology

Osmosis - YouTube 👍 43 👎 6

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Score: **22.4%**

1 ✓
2 ✓

PassMedicine

Question 411 of 414 ✗

Which one of the following hormones is under continuous inhibition?

Growth hormone	13%
🟩 Prolactin	68%
Gonadotropin releasing hormone	7%
Thyroid releasing hormone	5%
🟥 Adrenocorticotrophic hormone	7%

Prolactin - under continuous inhibition

Important for me Less important

The correct answer is **Prolactin**. Prolactin secretion from the anterior pituitary gland is primarily regulated by inhibition: the hypothalamus produces prolactin inhibitory factors (most notably dopamine), which are released into the hypophyseal portal bloodstream and bind to receptors on lactotrophs in the anterior pituitary, suppressing the release of prolactin. This inhibitory control is unusual among anterior pituitary hormones, which are primarily under stimulatory hypothalamic control.

Growth hormone is not continuously inhibited. Growth hormone secretion is regulated by two hypothalamic hormones, growth hormone-releasing hormone (GHRH) and somatostatin. GHRH stimulates GH release while somatostatin inhibits it. However, this does not mean that growth hormone is under continuous inhibition as these two hormones work together in a pulsatile manner to regulate its secretion.

Gonadotropin releasing hormone (GnRH) also does not fall under continuous inhibition. It's secreted in a pulsatile fashion from the hypothalamus, stimulating the pituitary gland to produce luteinising hormone (LH) and follicle-stimulating hormone (FSH). The levels of GnRH can be influenced by negative feedback mechanisms from sex steroids and inhibins but it's not under constant inhibition.

Similarly, **Thyroid releasing hormone (TRH)** isn't constantly inhibited either. TRH stimulates the pituitary gland to secrete thyroid-stimulating hormone (TSH), which then acts on the thyroid gland to produce thyroxine. While high levels of circulating thyroxine can inhibit TRH production through a negative feedback mechanism, this doesn't constitute continuous inhibition.

Finally, **Adrenocorticotrophic hormone (ACTH)** isn't under continuous inhibition. ACTH release from the pituitary gland is stimulated by corticotropin-releasing hormone (CRH) from the hypothalamus and inhibited by high levels of cortisol via negative feedback. However, this process doesn't constitute constant inhibition as ACTH secretion varies throughout the day with the highest levels in early morning and lowest at night.

👍 👎 Discuss (1) Improve

Next question

Prolactin and galactorrhoea ★

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. Dopamine acts as the primary prolactin releasing inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- prolactinoma
- pregnancy
- oestrogens
- physiological: stress, exercise, sleep
- acromegaly: 1/3 of patients
- polycystic ovarian syndrome
- primary hypothyroidism (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- metoclopramide, domperidone
- phenothiazines

- haloperidol
- very rare: SSRIs, opioids

Next question

Textbooks

High-yield textbook

Extended textbook

Links

Patient.info 👍 2 👎 1

Galactorrhoea review

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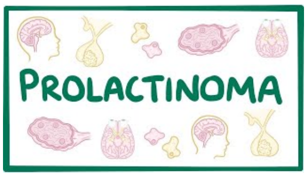
Media



Prolactinoma

Osmosis - YouTube 👍 15 👎 1

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PassMedicine

Question 412 of 414 ✗

A 69-year-old female with a history of multiple myeloma is admitted with confusion. The following results are obtained:

Na^+	147 mmol/l
K^+	4.7 mmol/l
Urea	14.2 mmol/l
Creatinine	102 µmol/l
Adjusted calcium	3.9 mmol/l

What is the most appropriate initial management?

	IV 0.45% saline	9%
	IV zoledronic acid	11%
	Oral prednisolone	3%
🟥	IV pamidronate	8%
🟩	IV 0.9% saline	69%

IV fluid therapy is the first-line management in patients with hypercalcaemia

Important for me Less important

The raised sodium is a function of dehydration and will correct once the patient is adequately rehydrated

Discuss (5) Improve

Next question

Hypercalcaemia: management ★

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

Loop diuretics such as furosemide are sometimes used in hypercalcaemia, particularly in patients who cannot tolerate aggressive fluid rehydration. However, they should be used with caution as they may worsen electrolyte derangement and volume depletion.

Next question

B *I*

Textbooks

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Links

Royal College of Physicians 👍 2 👎 3

Hypercalcaemia â€“ presentation and management

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Media

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Question 413 of 414 ✗

A 51-year-old woman is reviewed in the diabetes clinic. She was diagnosed with type 2 diabetes mellitus 12 months ago and still has poor glycaemic control (63 mmol/mol). She has recently had to stop taking gliclazide due to repeated episodes of hypoglycaemia and is only taking maximum dose metformin. Her BMI is 26 kg/m^2. What is the most appropriate next step in management?

Add either pioglitazone, a DPP-4 inhibitor or a SGLT-2 inhibitor	71%
Refer her for a laparoscopic gastric band	0%
Refer her for insulin therapy	3%
Add either a thiazolidinedione or exenatide	3%
Add either a DPP-4 inhibitor or exenatide	23%

The correct answer is to **add either pioglitazone, a DPP-4 inhibitor or a SGLT-2 inhibitor**. According to the UK guidelines, if a patient with type 2 diabetes has poor glycaemic control on maximum dose metformin and another oral agent is not contraindicated or not tolerated, the next step in management is to consider adding a third oral agent such as pioglitazone (a thiazolidinedione), a DPP-4 inhibitor, or an SGLT-2 inhibitor. These medications have different mechanisms of action that can help improve glycaemic control without causing significant hypoglycaemia.

Referring her for a **laparoscopic gastric band** would not be the most appropriate next step in this case. Although bariatric surgery can lead to significant improvements in glycaemic control for patients with type 2 diabetes and obesity, this patient's BMI of 26 kg/m^2 does not meet the criteria for bariatric surgery according to UK guidelines (BMI ≥35 kg/m^2 with obesity-related comorbidities).

Referring her for **insulin therapy** would also not be the most appropriate next step. Insulin therapy is typically considered when oral agents are no longer effective or contraindicated. However, in this case, there are still other oral agents available that could be tried before resorting to insulin therapy.

Adding either a **thiazolidinedione or exenatide** would only partially address the issue because pioglitazone is already an option as it belongs to the thiazolidinedione class. Exenatide, which is a GLP-1 receptor agonist, could also be considered but may not be preferred due to its injectable administration route and potential gastrointestinal side effects. The question's correct answer provides a broader range of options, including both oral and injectable agents.

Adding either a **DPP-4 inhibitor or exenatide** would again only partially address the issue. While DPP-4 inhibitors are an appropriate option, as mentioned earlier, exenatide may not be preferred due to its injectable administration route and potential gastrointestinal side effects. The correct answer offers a wider variety of treatment options that can help improve glycaemic control without causing significant hypoglycaemia.

Discuss (10) Improve

Next question

Diabetes mellitus: management of type 2 ★

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2022. This update reflected the advances in drug therapy and improved evidence regarding newer therapies such as SGLT-2 inhibitors.

> It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates
- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage the use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

HbA1c targets

This is an area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes*'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single-drug treatment

Management of T2DM	**HbA1c target**
Lifestyle	48 mmol/mol (6.5%)
Lifestyle + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

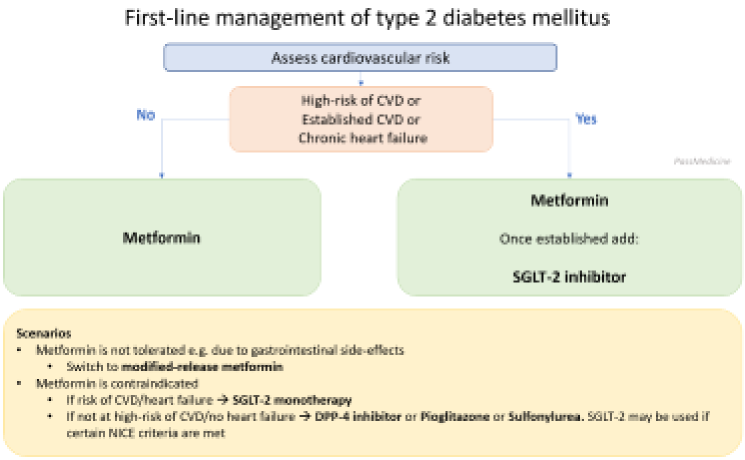
Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree on a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

Management of T2DM	**HbA1c target**
Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%)	53 mmol/mol (7.0%)

Initial drug therapy


First-line management of type 2 diabetes mellitus
Assess cardiovascular risk
High-risk of CVD or Established CVD or Chronic heart failure
No
Yes
PassMedicine
Metformin
Metformin
Once established add:
SGLT-2 inhibitor
Scenarios
Metformin is not tolerated e.g. due to gastrointestinal side-effects
Switch to modified-release metformin
Metformin is contraindicated
If risk of CVD/heart failure → SGLT-2 monotherapy
If not at high-risk of CVD/no heart failure → DPP-4 inhibitor or Pioglitazone or Sulfonylurea. SGLT-2 may be used if certain NICE criteria are met

Simplified initial management of type 2 diabetes mellitus

Metformin remains the first-line drug of choice in type 2 diabetes mellitus.

- metformin should be titrated up slowly to minimise the possibility of gastrointestinal upset
- if standard-release metformin is not tolerated then modified-release metformin should be trialled

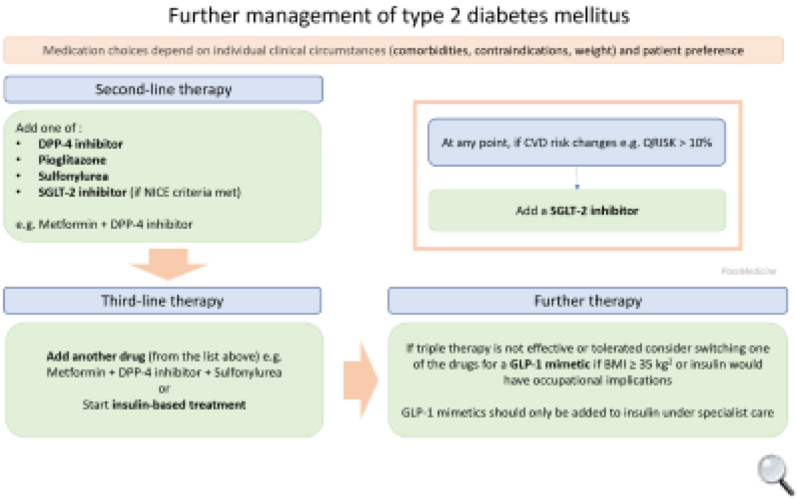
SGLT-2 inhibitors

- should also be given in addition to metformin if any of the following apply:
  - the patient has a high risk of developing cardiovascular disease (CVD, e.g. QRISK ≥ 10%)
  - the patient has established CVD
  - the patient has chronic heart failure
- metformin should be established and titrated up before introducing the SGLT-2 inhibitor
- SGLT-2 inhibitors should also be started at any point if a patient develops CVD (e.g. is diagnosed with ischaemic heart disease), a QRISK ≥ 10% or chronic heart failure

If metformin is contraindicated

- if the patient has a risk of CVD, established CVD or chronic heart failure:
  - SGLT-2 monotherapy
- if the patient doesn't have a risk of CVD, established CVD or chronic heart failure:
  - DPP-4 inhibitor or pioglitazone or a sulfonylurea
  - SGLT-2 may be used if certain NICE criteria are met

Further drug therapy if HbA1c targets are not met


Further management of type 2 diabetes mellitus
Medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference
Second-line therapy
Add one of :
DPP-4 inhibitor
Pioglitazone
Sulfonylurea
SGLT-2 inhibitor (if NICE criteria met)
e.g. Metformin + DPP-4 inhibitor
At any point, if CVD risk changes e.g. QRISK > 10%
Add a SGLT-2 inhibitor
Third-line therapy
Add another drug (from the list above) e.g. Metformin + DPP-4 inhibitor + Sulfonylurea or Start insulin-based treatment
Further therapy
If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic if BMI ≥ 35 kg² or insulin would have occupational implications
GLP-1 mimetics should only be added to insulin under specialist care

Simplified further management of type 2 diabetes mellitus if HbA1c targets are not met

If the HbA1c has risen to 58 mmol/mol (7.5%) then further treatment is indicated. Given the large number of drug therapy options, medication choices depend on individual clinical circumstances (comorbidities, contraindications, weight) and patient preference.

Second-line therapy

Dual therapy - add one of the following:

- metformin + DPP-4 inhibitor
- metformin + pioglitazone
- metformin + sulfonylurea
- metformin + SGLT-2 inhibitor (if NICE criteria met)

Third-line therapy

If a patient does not achieve control on dual therapy then the following options are possible:

- metformin + DPP-4 inhibitor + sulfonylurea
- metformin + pioglitazone + sulfonylurea
- metformin + (pioglitazone or sulfonylurea or DPP-4 inhibitor) + SGLT-2 if certain NICE criteria are met
- insulin-based treatment

Further therapy

If triple therapy is not effective or tolerated consider switching one of the drugs for a GLP-1 mimetic:

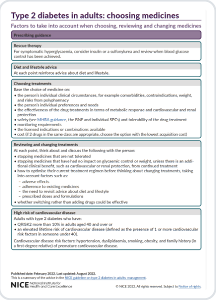
- BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

GLP-1 mimetics should only be added to insulin under specialist care

Starting insulin
- metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose-lowering therapies*'
- NICE recommend starting with human NPH insulin (isophane, intermediate-acting) taken at bed-time or twice daily according to need

Practical examples
- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have an HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea



Type 2 diabetes in adults: choosing medicines

Factors to take into account when choosing, reviewing and changing medicines

Prescribing guidance

Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Diet and lifestyle advice
At each point reinforce advice about diet and lifestyle.

Choosing treatments
Base the choice of medicine on:
- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- the person's individual preferences and needs
- the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection
- safety (see MHRA guidance, the BNF and individual SPCs) and tolerability of the drug treatment
- monitoring requirements
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)

Reviewing and changing treatments
At each point, think about and discuss the following with the person:
- stopping medicines that are not tolerated
- stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment
- how to optimise their current treatment regimen before thinking about changing treatments, taking into account factors such as:
  - adverse effects
  - adherence to existing medicines
  - the need to revisit advice about diet and lifestyle
  - prescribed doses and formulations
- whether switching rather than adding drugs could be effective

High risk of cardiovascular disease
Adults with type 2 diabetes who have:
- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

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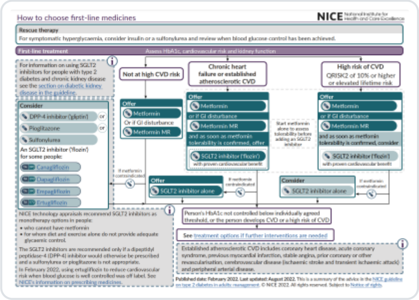

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Consider
DPP-4 inhibitor ('gliptin') or
Pioglitazone or
Sulfonylurea
An SGLT2 inhibitor ('flozin') for some people:
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

Not at high CVD risk
Offer
Metformin
Or if GI disturbance
Metformin MR

Chronic heart failure or established atherosclerotic CVD
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, offer
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk
Offer
Metformin
or if GI disturbance
Metformin MR
and as soon as metformin tolerability is confirmed, consider
SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

If metformin contraindicated

Offer
SGLT2 inhibitor alone

If metformin contraindicated

Consider
SGLT2 inhibitor alone

If metformin contraindicated

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:
- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

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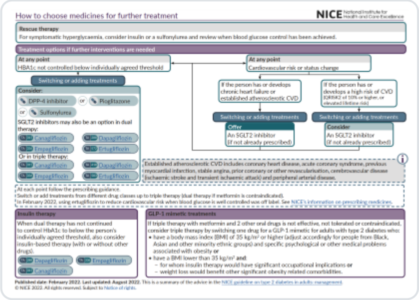

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point
HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider:
DPP-4 inhibitor or Pioglitazone
or Sulfonylurea
SGLT2 inhibitors may also be an option in dual therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin
Or in triple therapy:
Canagliflozin Dapagliflozin
Empagliflozin Ertugliflozin

At any point
Cardiovascular risk or status change

If the person has or develops chronic heart failure or established atherosclerotic CVD
Switching or adding treatments
Offer
An SGLT2 inhibitor (if not already prescribed)

If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk)
Switching or adding treatments
Consider
An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy
When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).
Dapagliflozin Empagliflozin
Canagliflozin

GLP-1 mimetic treatments
If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:
- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2 **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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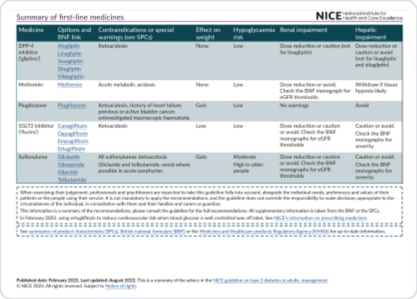

Summary of first-line medicines

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Dose reduction or caution or avoid (not for linagliptin and sitagliptin)
Metformin	Metformin	Acute metabolic acidosis	None	Low	Dose reduction or avoid. Check the BNF monograph for eGFR thresholds	Withdraw if tissue hypoxia likely
Pioglitazone	Pioglitazone	Ketoacidosis, history of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid. Check the BNF monographs for severity

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

This information is a summary of the recommendations, please consult the guideline for the full recommendations. All supplementary information is taken from the BNF or the SPCs.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) for up-to-date information.

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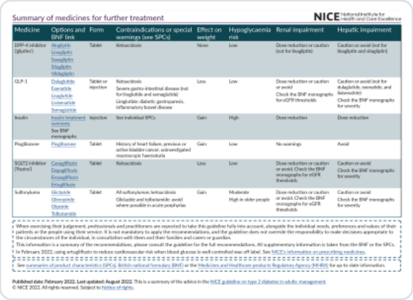

Summary of medicines for further treatment

NICE National Institute for Health and Care Excellence

Medicine	Options and BNF link	Form	Contraindications or special warnings (see SPCs)	Effect on weight	Hypoglycaemia risk	Renal impairment	Hepatic impairment
DPP-4 inhibitor ('gliptins')	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Tablet	Ketoacidosis	None	Low	Dose reduction or caution (not for linagliptin)	Caution or avoid (not for linagliptin and sitagliptin)
GLP-1	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Tablet or injection	Ketoacidosis Severe gastro-intestinal disease (not for liraglutide and semaglutide) Liraglutide: diabetic gastroparesis, inflammatory bowel disease	Loss	Low	Dose reduction or caution or avoid Check the BNF monographs for eGFR thresholds	Caution or avoid (not for dulaglutide, exenatide, and lixisenatide) Check the BNF monographs for severity
Insulin	Insulin treatment summary See BNF monographs	Injection	See individual SPCs	Gain	High	Dose reduction	Dose reduction
Pioglitazone	Pioglitazone	Tablet	History of heart failure, previous or active bladder cancer, uninvestigated macroscopic haematuria	Gain	Low	No warnings	Avoid
SGLT2 inhibitor ('flozins')	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Tablet	Ketoacidosis	Loss	Low	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity
Sulfonylurea	Gliclazide Glimepiride Glipizide Tolbutamide	Tablet	All sulfonylureas: ketoacidosis Gliclazide and tolbutamide: avoid where possible in acute porphyrias	Gain	Moderate High in older people	Dose reduction or caution or avoid. Check the BNF monographs for eGFR thresholds	Caution or avoid Check the BNF monographs for severity

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Risk factor modification

Hypertension

- **blood pressure targets are the same as for patients without type 2 diabetes** (see table below)
- ACE inhibitors or angiotensin II receptor blockers (ARB) are first-line
  - an ARB is preferred if the patient has a black African or African-Caribbean family origin

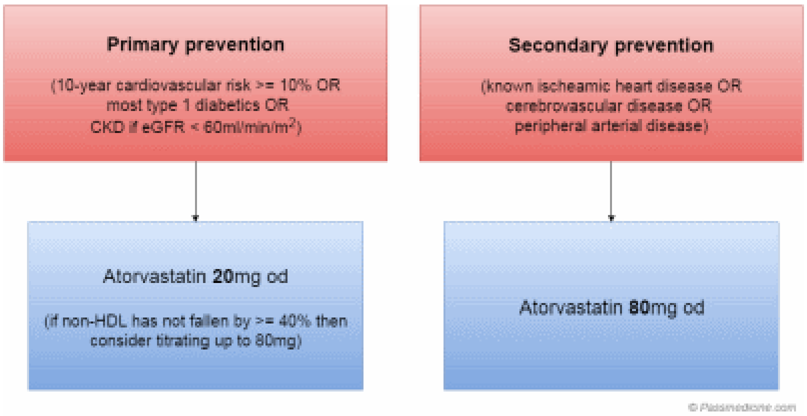
	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

Next question

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 3 👎 0

2014 Lipid modification guidelines

7 minute medics 👍 11 👎 4

Basics of type 2 diabetes - podcast

SIGN 👍 4 👎 2

2010 Management of diabetes

NICE 👍 8 👎 5

2022 Type 2 diabetes guidelines

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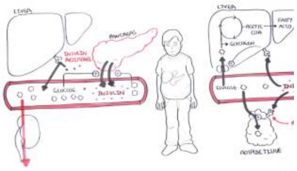
Media

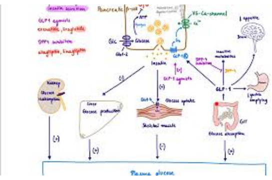


Diabetes Type II Pathophysiology

Armando Hasudungan - YouTube 👍 9 👎 1

Pharmacology of drugs used to treat type 2 diabetes

Brandl's Basics - YouTube 👍 17 👎 3



Type 2 diabetes agents and their mechanism of action

Brandl's Basics - YouTube 👍 18 👎 4

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Score: **22.3%**

1 ✓
2 ✓
3 ✓

PassMedicine

Question 414 of 414 ✗

A 75-year-old woman presents with urinary incontinence. She describes a sudden and very intense need to pass urine which is often followed by incontinence. She has a past medical history of Alzheimer's disease and closed-angle glaucoma.

What is the preferred treatment?

	Darifenacin	2%
🟥	Duloxetine	11%
🟩	Mirabegron	67%
	Oxybutynin	15%
	Tolterodine	5%

Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative

Important for me Less important

This is a classical case of urge incontinence.

Mirabegron is correct. Mirabegron (a beta-3 agonist) is the preferred agent in this case due to the side effect profile of anticholinergic agents.

Darifenacin, **Oxybutynin**, and **Tolterodine** are incorrect. These agents are all anti-muscarinic agents which can cause confusion and exacerbate closed-angle glaucoma.

Duloxetine is incorrect. This is the agent of choice for stress incontinence.

Discuss (1) Improve

Urinary incontinence ★

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors

- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification

- overactive bladder (OAB)/urge incontinence
  - due to detrusor overactivity
  - the urge to urinate is quickly followed by uncontrollable leakage ranging from a few drops to complete bladder emptying
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement
- functional incontinence
  - comorbid physical conditions impair the patient's ability to get to a bathroom in time
  - causes include dementia, sedating medication and injury/illness resulting in decreased ambulation

Initial investigation

- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:

- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line
  - NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation)
  - Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:

- pelvic floor muscle training
    - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures
- duloxetine may be offered to women if they decline surgical procedures
    - a combined noradrenaline and serotonin reuptake inhibitor
    - mechanism of action: increased synaptic concentration of noradrenaline and serotonin within the pudendal nerve → increased stimulation of urethral striated muscles within the sphincter → enhanced

contraction

Textbooks

High-yield textbook

Extended textbook

Links

NICE 👍 5 👎 6

2019 urinary incontinence guidelines

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Media

URINARY
INCONTINENCE